

**ANTIBIOTIC PROPHYLAXIS IN A PRIMARY LEVEL HOSPITAL: A MEDICINES  
USE EVALUATION TO ASSESS COMPLIANCE IN CAESAREAN SECTIONS**

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**BY**

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## ABSTRACT

**Introduction:** Caesarean section births are the most important known common factor that has been linked with post-partum bacterial infections. According to the current Standard Treatment Guidelines, the prophylactic dose in surgical prophylaxis is a single dose of cefazolin, equal to the standard therapeutic dose, and given as a single *stat* dose prior to surgery. Multiple-dose regimes are associated with higher costs compared to a single-dose regime, not just in terms of acquisition costs but also in terms of staff time.

**Aim:** To contribute to the rational use of antibiotics, through the application of a medicines use evaluation in a district hospital.

**Methods:** A retrospective Medicine Use Evaluation (MUE) was carried out at Heidelberg Hospital in Gauteng. The quantitative data was collected over a 3 month study period in which the medical records of 120 female patients who delivered through Caesarean section was captured using the Medicine Use Evaluation data sheet. The qualitative phase involved structured interviews with medical officers to establish reasons for non-compliance. A total of 7 medical officers participated in the interviews.

**Results:** None of the 120 patients received the stipulated regimen as recommended in The Standard Treatment Guidelines. Patients either received: 1 day of cefazolin, administered every 8 hours intravenously (83/120, 69.2%) or 3 days' of cefazolin administered every 8 hours (37/120, 30.8%). Every HIV-uninfected woman (83/120, 69.2%) received 3 doses of cefazolin, whereas every HIV-infected woman received 9 doses of cefazolin and metronidazole intravenously. All patients also received 5 days' of oral antibiotics on discharge. Eighty-five percent of patients did not have a justifiable reason for receiving a full therapeutic course.

**Discussion:** Clear evidence was provided that the administration of antibiotic prophylaxis for Caesarean section deliveries at Heidelberg Hospital was irrational. Using MUE methods, the study identified different elements of non-compliance with the national recommendations. The study did not provide any justifications for the therapeutic use of antibiotics in patients without established or suspected infections post-operatively.

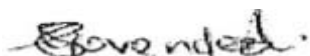
**Recommendations:** The Standard Treatment Guidelines should provide unambiguous recommendations for the use of prophylaxis in women undergoing Caesarean sections in addition to the management of women suspected of having an established infection, and who deserve a full therapeutic course of antibiotics.

## DECLARATION

In fulfilment of the requirements of the degree of Master of Pharmacy (Pharmacy Practice) in the Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa, I, Seshnee Govender, declare that:

- i. The research reported in this dissertation, except where referenced, is my original work.
- ii. This dissertation has not been submitted for any degree or examination at any other university.
- iii. This dissertation does not contain other person's data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
- iv. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
  - a. their words have been re-written but the general information attributed to them has been referenced:
  - b. where their exact words have been used, their writing has been placed inside quotation marks, and referenced.
- v. Where reference to a publication for which I am a principal author, I have referenced the "In Press" publication.

Student Signature: \_\_\_\_\_



Date: 22 November 2016

## **DEDICATION**

Success is the fruit of personal effort and perseverance together with the love and support I was so fortunate to receive throughout this journey. This dissertation is in honor of my parents, Saras and Sagren Govender, whom I am so blessed to have in my life, I am eternally grateful for your unwavering love and motivation. As with any task, this dissertation would not have not materialised if it was not for the grace and blessings of God, for which I am humbled by. To my amazing sister, Dersnee, who is my pillar of strength, my rock and best friend, thank you for the encouragement and motivation that pushed me to complete this dissertation. To Marcus, I am grateful for your incomparable love, kind heart and constant support, you have played a pivotal role in my achievements.

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## ACRONYMS AND ABBREVIATIONS

ADRs	Adverse drug reactions
AIDS	Acquired immunodeficiency syndrome
AMR	Antimicrobial resistance
ART	Antiretroviral therapy
ASHP	American Society of Health-System Pharmacists
ASPs	Antimicrobial stewardship programmes
BMI	Body mass index
CPD	Cephalopelvic disproportion
CS	Caesarean section
EML	Essential Medicines List
HIV	Human immunodeficiency virus
iMMR	Institutional Maternal Mortality Ratio
IV	Intravenous
LOS	Length of stay
MCG	Maternal Care Guidelines
MDG	Millennium Development Goal
MMR	Maternal mortality ratio
MUE	Medicines use evaluation
NDOH	National Department of Health
NEMLC	National Essential Medicines List Committee
PROM	Premature rupture of membranes
PRS	Pregnancy-related sepsis
SAP	Surgical antibiotic prophylaxis
SDG	Sustainable Development Goals
SSI	Surgical site infection
STG	Standard Treatment Guideline
WHO	World Health Organization

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## **CHAPTER I: INTRODUCTION**

This chapter provides the overall context for the study, locates it within the overall health system and the theoretical background, and then lists the aim and specific objectives.

### **1.1 Health and healthcare delivery in South Africa**

The health system in South Africa is comprised of the public health sector, which is funded by the state and serves approximately 83% of the population, and the private for-profit sector, which is better resourced, usually funded by the subscriptions of individuals to medical aid schemes and serves approximately 17% of the population (Council for Medical Schemes Annual Report, 2015). Public health utilised an estimated 15% of the government's total budget in 2015, most of which was allocated to the nine provincial departments via the equitable share mechanism (Day and Gray, 2016). The total expenditure on health as a percentage of the Gross Domestic Product (GDP) in 2015 was 8.5%, with almost half each expended in the public and private sectors, respectively (Day and Gray, 2016). Given the levels of impoverishment and unemployment in South Africa, the greater burden of healthcare (if not expenditure) continues to remain the responsibility of the Department of Health, provided mainly through the public sector.

Due to the burden of disease in South Africa, the treatment and prevention of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) and tuberculosis (TB) consumes a large proportion of national expenditure. More than 70% of all persons living with HIV in the world are in sub-Saharan Africa, with 6.19 million South Africans (11.2% of the population) living with HIV (Jobson, 2015). The national antenatal HIV prevalence in South Africa was 29.7% in 2015, with the highest prevalence (42.5%) in pregnant women aged 30-39 years (South African National Department of Health, 2015). In 2015, Statistics South Africa estimated that 531 965 people died, with 30.5% of these deaths being AIDS-related (Statistics South Africa, 2015). This can impact negatively on the country if economically active people are dying, thus leaving their children to fend for themselves. In 2015, R15.9 billion from the health budget was utilised for HIV treatment and prevention and R740 million for the treatment of tuberculosis, including enhanced screening and earlier detection and diagnosis (Day and Gray, 2016).

The public sector faces considerable human resource constraints (Jobson, 2015). Positive accomplishments of the past decade are largely overshadowed by the burden of AIDS on mortality and the health system. Certainly, the management of the HIV and AIDS epidemic will continue to dominate the next decade and beyond. Efforts to sustain financing for the prevention and treatment of HIV and AIDS, while improving service efficiency and quality of care, will require new funding formulas such as those envisaged in a National Health Insurance system (Minister of Health, 2015). However, despite the extent of the challenge there are opportunities for considerable systems improvements and advancement in relation to the major policy priorities (Harrison, 2009).

### ***1.1.1 The public healthcare system***

Care is delivered through different levels in the public healthcare system in South Africa. The basis of the public health system is the primary healthcare clinics, which are the first line of access for patients requiring healthcare services at no cost. Accessibility of primary healthcare facilities has improved over the years, although there are some reports that the quality of service provided has declined. District hospitals are generally the next level of healthcare. Patients are referred to the district hospitals from primary healthcare clinics when they require more sophisticated treatment. More sophisticated care available at district hospitals is provided through regional hospitals. The tertiary level includes the central or academic hospitals, where even more specialised treatment and advanced diagnostic procedures are available. These academic hospitals also serve as training institutions for healthcare providers (Jobson, 2015). Lastly, there are specialised hospitals, such as those providing psychiatric and tuberculosis services. According to Jobson (2015), there were 4200 public health facilities in South Africa in 2015, with each clinic providing on average for 13 718 persons (a figure that exceeds the WHO guidelines of 10 000 per clinic). Jobson also noted that the public-sector dependent population averaged 2.5 visits per year to public health facilities and that bed occupancy rates in public sector hospitals were between 65% and 77%. Since 1994, more than 1600 clinics have been built or upgraded. For 2.5 million South Africans, their nearest clinic is more than 5 kilometres away from their homes.

There were 376 public hospitals in the country in 2015, of which 143 were in urban areas and 233 in rural areas (Jobson, 2015). In 2015, R31.9 billion of the health budget was utilised for primary healthcare services and R88.2 billion for hospital care (Day and Gray, 2016). Sixty-four

percent of public hospitals were district hospitals, with regional and specialised hospitals making up 16% each of the total number. Together academic and central hospitals made up less than 4% of all hospitals in the public sector (Jobson, 2015). For most South Africans, in particular those in rural areas, district hospitals are the only hospitals to which they would most likely get admitted. A district hospital has a 24-hour emergency service and an operating theatre. This is the first level of referral and generalist staff (ordinary medical officers, as opposed to medical specialists) are available with access to basic diagnostic and therapeutic services, such as basic radiography and basic laboratory tests. A functional operating theatre would be present in which operations are performed regularly under general anaesthesia (although there would be no specialist anaesthesiologist available). However, there would be no intensive care unit. According to the World Health Organization's (WHO) functional definition, district hospitals should provide diagnostic, treatment, care, counselling and rehabilitation services. They should cover the following clinical disciplines at generalist level: family medicine and primary healthcare, internal medicine, obstetrics, psychiatry, rehabilitation, surgery, paediatrics and geriatrics (Cullinan, 2006).

### ***1.1.2 The private healthcare system***

The private healthcare system on the other hand provides services on a for-profit basis, mostly by self-employed health professionals. These services are usually funded by the subscriptions of individuals to medical aid schemes, supplemented by employer contributions. There were 238 private hospitals in the country in 2015, of which 188 were in urban areas and 50 in rural areas (Jobson, 2015). The private healthcare sector covered approximately 17% of the population in 2015. The medical aid schemes covered the needs of just over 8.8 million beneficiaries and received R140.2 billion worth of contributions (Council for Medical Schemes Annual Report, 2015; Day and Gray, 2016).

## **1.2 From the Millennium Development Goals to the era of Sustainable Development Goals**

In September 2015, the UN General Assembly adopted "Transforming our World: The 2030 Agenda for Sustainable Development", a plan outlining a new framework to replace the Millennium Development Goal (MDG) structure with the new Sustainable Development Goals (SDGs) (United Nations, 2015a). The SDGs comprise of 17 universal goals, with 169 targets and 230 indicators leading up to 2030. These goals are intended to build on the momentum and

enthusiasm generated by the MDGs, but also to reframe them within the context of a broader range of environmental and societal challenges (Griggs *et al.*, 2013). The Global Strategy for Women's, Children's, and Adolescents' Health 2016–2030 has aimed to highlight the global discussion of maternal mortality, with a variety of programmes which are aimed at improving the health of women and children (WHO, 2016a). Health is a core dimension of the SDGs, with SDG 3 aiming to “ensure healthy lives and promote well being for all at all ages”.

As the MDG era has now reached its end and the SDG era is commencing, it is worth reflecting on the degree of global, regional, and national progress toward MDG 5, the specific MDG that targeted maternal health. Whereas MDG 5 set a target of reducing the maternal mortality ratio (MMR; defined as the number of maternal deaths per 100 000 livebirths) by 75% between 1990 and 2015, SDG 3.1 sets a specific target for all countries to lower MMR to less than 70 by 2030 (GBD 2015 Maternal Mortality Collaborators, 2016). In 2015, an estimated 303 000 global maternal deaths occurred, representing a 44% reduction from 1990. Sub-Saharan Africa had the most maternal deaths, accounting for 201 000 (66%) maternal deaths globally, with southern Asia accounting for 66 000 (22%) maternal deaths. The African share has seen a drastic increase from 42% in 1990 to 66% in 2015. While maternal mortality has declined globally, South Africa was one of the three countries which showed an increased MMR, with 6.4% of maternal deaths suspected to be HIV-related. The impact of high fertility rates, poor maternal health systems, and low perinatal survival are apparent (Graham *et al.*, 2016). In South Africa, the number of maternal deaths increased from 1558 to 1754 between 1990 and 2015 and the maternal mortality ratio increased from 153.8 to 157.9 per 100 000 livebirths between 1990 and 2015 (GBD 2015 Maternal Mortality Collaborators, 2016). The GBD project has predicted that “as immediate mortality continues to decrease as a result of improved antenatal, obstetric, and post-partum care, it is therefore increasingly likely that the proportion of late maternal deaths will continue to increase” (GBD 2015 Maternal Mortality Collaborators, 2016). In 2015, 61.2% of 188 countries had already achieved the SDG target for MMR (GBD 2015 SDG Collaborators, 2016).

The quantitative effect of MDG 5 is difficult to measure, but it is clear that it united the international community in striving to decrease maternal mortality. With the endorsement of SDG 3.1 and SDG 3.7, and better quality data, health systems will need to make informed decisions about how to prioritise actions needed to bring about further improvement. The steps that have been suggested include making changes to the cause of death data collection systems and the dissemination of data together with more effective and extensive action and policies to

promote young girls and women having accessible education, making comprehensive family planning services available, and ensuring that different types of reproductive care are made accessible to each and every woman for them to survive (GBD 2015 SDG Collaborators, 2016). In order to achieve the reproductive healthcare targets outlined in SDG 3.7.5, the international community will have to pay attention to the intricately related issues of “immigration, armed conflicts, epidemics and pandemics, environment, economic instability, and gender equality”, all of which can have considerable effects on the availability and quality of reproductive health services and the willingness of women to seek them (GBD 2015 SDG Collaborators, 2016). As much as there is global progress with regard to reducing maternal mortality, which has been accelerating in the past 15 years, a substantial amount of work is still left to complete. As explained by the GBD 2015 SDG Collaborators (2016): “more than 250 000 women died during or following pregnancy in 2015, most of which were preventable deaths”. In South Africa the total number of maternal deaths increased from 1249 in 2010 to 1270 in 2014 (Day and Gray, 2016).

Some of the issues that need to be flagged as priorities are the poor skills of healthcare providers, low facility capability in terms of diagnostic tools and equipment, and inadequate lengths of stay. In a study by Campbell *et al.* (2016), the authors reported that most of the studied facilities in sub-Saharan Africa were badly equipped to provide emergency obstetric care services, in particular facilities at lower levels of the health system. There is a substantial room for improvement to provide respectful care of high quality in order to ultimately improve patient and healthcare provider satisfaction (Campbell *et al.*, 2016).

### **1.3 Antimicrobial stewardship programmes and management of resistant organisms**

The development of antimicrobials has been described as “one of the great landmarks of modern medicine” (Domínguez *et al.*, 2016). Although this has enabled a significant reduction in morbidity and mortality associated with microbial infections, it has also created a vicious cycle, in which the indiscriminate and inappropriate use of antimicrobials in both humans and animals has become associated with increased costs for treatments, risks of unwanted side effects and, more importantly, the emergence of antimicrobial resistance (Domínguez *et al.*, 2016).

Antimicrobial resistance (AMR) is an emerging public health threat which has managed to draw the attention of national and international organisations. The World Health Organization has defined the emergence of AMR as an increasingly serious threat to global public health that



requires action across all government sectors and society (WHO, 2015). There are several factors that have contributed to the spread of AMR in many communities. One contributing factor in particular, that has been frequently discussed, is the misuse or overuse of antibiotics in human medicine (Laxminarayan *et al.*, 2013). Existing estimates show that between 25%–50% of hospitalised patients receive antibiotics, with between 30% and 50% of antibiotic use being considered to be inappropriate (Dellit *et al.*, 2007). Published literature reveals a direct link between antibiotic use and the development of resistance (Goossens *et al.*, 2005; Aldeyab *et al.*, 2012; Livermore *et al.*, 2013).

A recent World Health Organization report on surveillance of resistance to antibacterial agents in bacteria commonly associated with hospital and community infections has revealed increased resistance and/or decreased susceptibilities (WHO, 2014). It was reported that the resistance of *Escherichia coli* to third-generation cephalosporins and fluoroquinolones and that of *Staphylococcus aureus* to methicillin was 50% or more in five out of the six WHO regions. *Klebsiella pneumoniae* resistance to third-generation cephalosporins was reported to be greater than 50% in all six WHO regions. Carbapenem-resistant *K. pneumoniae* was reported in all WHO regions, with reports in two regions exceeding 50%. It was further reported that the non-susceptibility of *Streptococcus pneumoniae* to penicillin was more than 50% in all six WHO regions (WHO, 2014; Akpan *et al.*, 2016). A similar AMR surveillance report from England revealed increased resistance of *E. coli* and *K. pneumoniae* to ciprofloxacin, third-generation cephalosporins, gentamicin, and both imipenem and meropenem (Akpan *et al.*, 2016). The same report, however, indicated decreased resistance of *Pseudomonas aeruginosa* to ceftazidime, gentamicin, and imipenem/meropenem. Recent reports stress that patients who have been infected by antibiotic-resistant bacteria have a two-fold increase in mortality as opposed to those infected with sensitive bacteria (Akpan *et al.*, 2016).

As a result of the lack of investment in research and development and the dearth of new antibacterials, a bleak future for the treatment of infections caused by multi-resistant bacteria has been predicted (Domínguez *et al.*, 2016). The progressive contraction in the number of available alternative antimicrobials has led to the "re-discovery" of older antimicrobials whose use had virtually been abandoned for various reasons, including toxicity. In this regard, colistin provides a prominent recent example. It is therefore of utmost importance that monitoring of antimicrobial consumption, both in the community and in the hospital setting, coupled with continuing education about the proper use of these scarce resources, is practised at all times (Domínguez *et al.*, 2016). Monitoring the consumption of antimicrobials in hospitals is particularly important, both to evaluate the factors that determine antimicrobial consumption as

well as to evaluate the impact of substituting antibiotics in cases of shortage, which might also influence the development of bacterial resistance (Domínguez *et al.*, 2016).

Antimicrobial stewardship programmes (ASPs) are intended to address all of the contributory factors to misuse and overuse of antibiotics (Johannsson *et al.*, 2011). Many hospital programmes may adopt restrictive measures as well as persuasive interventions such as audit and feedback methods (Davey *et al.*, 2013). Extensive surveillance of antimicrobial consumption thus forms a core part in many ASPs. The methods used may vary in different institutions but the outcome of reducing the emergence of resistance remains common. It has been claimed that there is no conclusive evidence that a decline in antibiotic use necessarily results in reduced antimicrobial resistance (Holmes *et al.*, 2016). Certainly, it is imperative to monitor patient outcomes when embarking on ASPs in order to ensure that individual patients' health is not harmed through either restrictive or persuasive policies.

Lanbeck *et al.* (2016) have highlighted that it is vital to analyse the economic consequences of ASPs, to make sure that decisions to introduce ASPs can be objectively compared with other potential efforts. Hence the implementation and operational costs need to be considered. The full health-economic consequences of ASPs are complex to calculate due to uncertainties about long-term effects on costs and benefits, as well as due to uncertainties in attributable costs and effects of the infection, which most commonly increase the length of stay in the hospital (Lanbeck *et al.*, 2016).

ASPs function best when they are motivated by quality considerations and are focused on improving the use of antibiotics in healthcare institutions. An ASP is essentially a programme aimed at optimising clinical outcomes and minimising unintended consequences (Dellit *et al.*, 2007). Proposed strategies to achieve these goals have included prospective audit with intervention and feedback, formulary restriction and pre-authorisation, education, guidelines and clinical pathways, antimicrobial cycling and scheduled antimicrobial switch programmes, specific antimicrobial order forms, automatic stop orders, recommending combination therapy, streamlining or de-escalation of therapy, dose optimisation, conversion from parenteral to oral therapy (IV to oral switch), computer surveillance and the provision of decision support (Owens, 2008). A multidisciplinary team approach is required for an effective ASP, bearing the main responsibility for promoting prudent antimicrobial use. As recommended by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) ASP guidelines, this multidisciplinary team should consist of a medical practitioner and a clinical pharmacist with adequate infectious diseases training as core

members (Dellit *et al.*, 2007). The inclusion of a clinical microbiologist, information system specialist, infection control specialist, hospital epidemiologist, and hospital administrator is considered optimal. Healthcare organisations are also encouraged to develop quality measures or indicators to monitor and evaluate the impact of their ASPs (Akpan *et al.*, 2016).

According to a review by Smaill and Hofmeyr (2002), in women undergoing Caesarean sections, there is evidence to suggest the alteration of the cervicovaginal flora, regardless of the use of antibiotics. However in the past this did not cause a problem with managing resistant organisms (Galask, 1987). The development of antibiotic resistance may now be a factor with the widespread use of antimicrobial prophylaxis (Shlaes *et al.*, 1997). There are no data to support the contention that correct use of a short course of antimicrobial prophylaxis will cause significant bacterial resistance nor evidence that a policy of strictly enforced and restricted antibiotic prophylaxis for CS has harmful effects that outweigh its benefits, even in those women perceived to be at low risk. One of the recommendations to avoid antimicrobial resistance is to place emphasis on optimising the choice and the duration of prophylactic antibiotics (Shlaes *et al.*, 1997). Careful monitoring of trends in antibiotic resistance should be used to establish appropriate practice guidelines and to monitor the impact of institutional policies. Susceptibility testing of significant bacterial isolates should be used as a guide for treatment in women who develop infection, despite the provision of appropriate prophylaxis (Smaill and Hofmeyr, 2002).

#### **1.4 Caesarean section as a means of delivery**

Caesarean section (CS) was introduced into obstetric practice as a life saving procedure both for the mother and the baby. As with other procedures of similar complexity, “its use follows the healthcare inequity pattern of the world: underuse in low income settings, and adequate or even unnecessary use in middle and high income settings” (WHO, 2010). Numerous studies have shown an inverse relationship at population level between CS rates and maternal and infant mortality in low-income countries where most sectors of the population do not have access to basic obstetric care (Betrán *et al.*, 2007, Althabe *et al.*, 2006, Ronsmans *et al.*, 2006). However, other studies have shown that there is no additional benefit for both the mother and baby if CS rates are above a certain limit, and high CS rates could result in negative consequences in both maternal and child health when indicated inappropriately, as the potential harm may exceed the potential benefit of the CS (WHO, 2010).

Obstetric factors occurring around birth were reported to be the main reasons leading to CS delivery. In a study by Abebe *et al.* (2016), the major obstetric indications for women who delivered by CS were obstructed labour (30.7%), foetal distress (15.9%) and abnormal presentation (13.4%). However with the currently available option of elective CS, rates of CS have steadily increased in most middle- and high-income countries without medical justification. According to the Guidelines for Maternity Care in South Africa (2016) the indications stated for elective CS delivery were triplets (or higher order pregnancy), intrauterine growth restriction, first twin breech or transverse lie after 37 weeks, or previous Caesarean section. Maternal request is one of the frequent factors contributing to the trend towards higher CS rates, resulting in obstetricians facing high demands for non-medically indicated CS (Department of Health, 2016).

In general, the inability of health services to offer necessary CS in non-urban and under-resourced settings is a growing problem globally. However, sharp increases in CS rates in some developing countries, especially in Latin America, have become a major problem. Data available for Brazil show that the overall rate of CS for that country is 30%, reaching as high as 50% in certain provinces (Barros *et al.*, 1991, Faundes and Cecatti, 2005). In this situation, other factors including malnutrition and poor social conditions are likely to exacerbate the already higher risk of infectious morbidity and mortality associated with CS. Another serious concern is the fact that a considerable number of CS are unnecessary and are planned in advance, with the additional potential risk of iatrogenic prematurity (Cecatti, 2005).

In 1985, the WHO stated that there is no justification for any region to have CS rates higher than 10-15% (WHO, 1985). The WHO assessed the prevalent CS rates in 2008 in 137/192 United Nations member states, representing 95% of global births (WHO, 2010; UNICEF, 2008) and reported that approximately 18.5 million CS were performed globally each year, with approximately 40% of countries having CS rates <10%, about 10% having CS rates between 10 and 15%, and approximately 50% having CS rates >15%. With regard to the 15% target, an estimated 6.2 million CS were performed in excess of this target per annum. China and Brazil accounted for almost 50% of the total number of unnecessary CS (WHO, 2010). The WHO further stated that, from a population-based approach, the indications for the excess number of CS were not likely to be medically warranted. The 15% upper limit suggested by WHO in 1985 has however been challenged. For example, in high-income countries, older women delivering for the first time and babies with increased birth weight may require more CS. However, the

WHO nevertheless highlighted that current studies have demonstrated thus far that there is no evidence of benefit for the health of mothers and babies in populations with values of CS above 15% (WHO, 2010). With regard to the lower limit, it has been argued that CS rates as low as 5% could possibly achieve major improvement in maternal outcomes (WHO, 2010).

Given the growing numbers of women who deliver through CS, the choice of the most appropriate and effective prophylactic antibiotic is of utmost importance. In such cases, as an attempt to reduce the cost for the health system, it would be advisable to have a “simple and inexpensive recommended antibiotic regimen” (Cecatti, 2005). A major limitation of the available literature on antimicrobial prophylaxis for all types of surgery is the difficulty in establishing significant differences in efficacy between prophylactic antimicrobial agents and controls (including placebo, no treatment, or other antimicrobial agents) due to study design and low surgical site infection (SSI) rates for most procedures (Bratzler *et al.*, 2013).

#### ***1.4.1 Caesarean section rates in South Africa***

From a national perspective in South Africa, the CS rates in both the public and private sectors appear to be increasing at an alarming rate. CS rates for 2014 were reported to be 24.7% in the South African public sector (Day and Gray, 2016). This was considerably higher than the 20.6% reported in 2008 (WHO, 2010). The highest CS rates in 2014 were recorded for KwaZulu-Natal (29.5%), but rates were also high in Gauteng (25.5%) (Day and Gray, 2016). Higher rates may have been recorded in these provinces due to the provision of services to patients referred from more rural provinces to the tertiary and regional public hospitals in the better resourced provinces.

In South Africa, CS rates are much higher in the private sector than in the public sector, increasing from an alarming rate of 67.5% in 2013 to 70.8% in 2014 (Day and Gray, 2016). That said, the availability of studies that provide comparative figures for CS rates in the private and public health sectors in South Africa is limited (Naidoo and Moodley, 2009).

A retrospective clinical survey was carried out by Tshibangu *et al.* (2002), comparing CS deliveries in the private sector with those in teaching and public hospitals in Gauteng, South Africa. They reported, on average, a CS rate of 57% (11 572 CS in 20 151 deliveries) at six

private hospitals over a three-year study period compared to a CS rate of 28% and 19% in one teaching hospital and 20 public hospitals respectively.

Current available data from well-resourced countries suggest that morbidity and mortality for both mother and baby arising from CS are higher when compared with vaginal delivery (Snyman, 2002). In a study by Naidoo and Moodley (2009), CS rates in the private sector in KwaZulu-Natal were reported as 60.4%. This elevated CS rate was in accordance with trends seen in countries such as those in South America, and was considerably higher than the ideal rate of 10 to 15% in low-risk obstetric populations as suggested by the WHO (Naidoo and Moodley, 2009). The high rates of CS found in the study by Naidoo and Moodley (2009) are probably a reflection of the trend in South Africa.

### **1.5 Problem statement**

The Standard Treatment Guidelines (STGs) issued by the National Department of Health (NDOH) are intended to provide practitioners in the public sector with a standardised approach to the rational, safe, and effective use of antimicrobial agents for the prevention of surgical-site infections (SSIs), based on currently available clinical evidence. There has been evidence of non-compliance with the South African national guidelines at Heidelberg Hospital, a district level government hospital with a small maternity ward. According to the STGs, the prophylactic dose in CS is a single dose of intravenous cefazolin equal to the standard therapeutic dose. A second dose is only administered should surgery be prolonged (National Department of Health, 2012). As highlighted in the peer-reviewed literature, there is no added benefit of using multiple doses over single dose of antibiotics for prophylaxis of SSI (Shakya and Sharma, 2010; Slobogean *et al.*, 2010) and antibiotic prophylaxis should be given as a single dose (Lyimo *et al.*, 2013).

The research question is therefore: in women undergoing Caesarean sections at Heidelberg Hospital, is the correct choice of antibiotic and duration of antibiotic prophylaxis being administered, in accordance with the current South African National Department of Health (NDOH) Standard Treatment Guidelines (STG), and if not, what are the reasons for this non-compliance?

## **1.6 Purpose of the research**

The purpose of this study was to highlight the level of non-compliance, with the ultimate aim of identifying appropriate remedial action and either reconsideration of local practice or proposals for amendment of the NDOH STG. The goal of this retrospective action research was not only to elicit knowledge but to also bring about action that will benefit the patients as well the healthcare sector. In addition to contributing to the rational and responsible use of medicines, in particular antibiotics, through the application of medicines use evaluation (MUE), the purpose of the research was to help healthcare facilities to understand, interpret and improve the prescribing, administration and use of medications. This study therefore set out to provide potential reasons to reconsider the duration of prophylaxis stipulated in the national guidelines, which are not specific to CS (being directed at pelvic surgery in general). This MUE provided authorised prescribers with feedback on their prescribing patterns with respect to treatment protocols in the STG. The study also helped in improving the prescribing and administrations of antibiotics at the facility of focus.

## **1.7 Aim and objectives of the study**

### ***1.7.1 Overall aim***

The aim of this study was to contribute to the rational and responsible use of medicines, in particular antibiotics, through the application of medicines use evaluation in order to help healthcare facilities to understand, interpret and improve the prescribing, administration and use of medications, in a primary level hospital setting.

### ***1.7.2 Specific objectives***

The specific objectives were:

- to use Medicine Use Evaluation (MUE) methods to determine the degree to which local practice is in compliance with the national STG, with regards to antibiotic prophylaxis in CS, over a 3 month period, using retrospective data;
- to identify the reasons for any identified non-compliance with the national STG, by means of local document review and key informant interviews;

- to determine the average medicine costs associated with identified non-compliance with the national STG;
- to identify appropriate remedial actions to be taken on the basis of the results obtained during the study period; and
- to utilise the data obtained from the study to review and possibly implement new local hospital policies, and if sufficient evidence emerged, to possibly review the national STGs.

## **1.8 Summary**

This chapter has provided an outline of the relevant issues pertaining to the healthcare systems in South Africa as well as the dire need to address maternal mortality. It also provided an overview of antibiotic prophylaxis used in Caesarean sections in addition to the importance of antimicrobial stewardship programmes. The chapter also included the problem statement, purpose of the research, aim and, finally, the specific objectives of the study. The following chapters provide a literature review in Chapter 2, the methods used in the study in Chapter 3, a presentation of the results in Chapter 4, then an analysis and discussion of the results in Chapter 5 followed by the recommendations and conclusions of the study in Chapter 6.



## **CHAPTER II: LITERATURE REVIEW**

### **2.1 Introduction**

This chapter provides a summary of the available literature that has been reviewed to further elaborate on the issues mentioned in Chapter 1. This chapter highlights the risk factors for surgical site infections and the common pathogens observed to be causing infections as well as give an overview of maternal mortality. The association of HIV and the risk of sepsis are highlighted. Emphasis is also placed on the importance of antimicrobial stewardship plans and the threat of antibiotic overuse, the challenges to measuring antimicrobial use, the need for specific measures in specific settings due to overuse as well as the need for research on stewardships. Medicine Use Evaluation is discussed, in terms of the different approaches (prospective, concurrent and retrospective). The theoretical framework of the study is also provided. The chapter is concluded with a chapter summary.

### **2.2 Risk factors for surgical site infections**

Caesarean section (CS) wound infections signify a considerable burden to the health system (Nwankwo *et al.*, 2012). According to the global estimates of surgical site infections (SSI), they account for between 0.5–15% of such infections (Arabashahi and Koohpayezade, 2006), varying according to the study population, the study design used to identify the cases, and the use of appropriate antibiotic prophylaxis (Mitt *et al.*, 2005). Surgical site infection following CS delivery has been implicated as an important cause of morbidity and mortality, leading to an increased duration of patient hospitalisation and hospital costs (Oliveira and Ciosak, 2004). Deliveries through CS have been associated with escalating rates of maternal morbidity, including venous thromboembolism, shock, and haemorrhage (Kuklina *et al.*, 2009). Hence, several comprehensive initiatives have been identified by obstetric organisations to lower the rates of maternal morbidity by addressing unnecessary CS (Dahlke *et al.*, 2013).

Post-operative length of stay (LOS) following non-obstetric surgery is an important quality indicator of inpatient care (Raleigh *et al.*, 2008). With regard to CS deliveries, LOS can also be used as a vital metric to evaluate the quality of obstetric care peri-partum and post-partum. Sadly, there are limited studies which investigate the risk factors linked to prolonged LOS after

a CS delivery. Such data could prove to be beneficial as it could aid ongoing efforts aimed at reducing maternal morbidity following CS delivery and could further be helpful for evaluating post-CS LOS as a quality measure related to obstetric practice (Blumenfeld *et al.*, 2015).

In the article by Blumenfeld *et al.* (2015), numerous maternal, medical, and obstetric characteristics associated with extended post-partum LOS were recognised: body mass index (BMI)  $\geq 40 \text{ kg/m}^2$ ; chronic condition such as diabetes, asthma and hypertension, multiple pregnancy;  $\geq 1$  prior Caesarean; and pregnancy-associated hypertensive disorders. Also, particular peri-operative morbidities were identified, including general anaesthesia, uterine atony, transfusion, hysterectomy, endometritis, ileus, wound complications. Perinatal factors associated with extended LOS were preterm delivery, neonatal birth weight. Peri-operative morbidities such as ileus, endometritis, and wound complications as well as surgery related complications, had the highest risk for prolonged post-partum LOS (Blumenfeld *et al.*, 2015). Blumenfeld *et al.* (2015) also showed that obese women were at higher risk of intra-partum morbidity, prolonged LOS, and wound complications when undergoing CS delivery. Similarly, a significant association was shown in women with a BMI  $>35 \text{ kg/m}^2$ , who were shown to be three times more likely to develop a wound infection as opposed to non-obese women (Dhar *et al.*, 2014). Increased rates of morbidity associated with post-CS endometritis, ranging from 16.9% to 32%, have been reported in other studies (Andrews *et al.*, 2003). Other well documented independent risk factors for post-CS SSI have included young age, hypertension or preeclampsia, chorioamnionitis, nulliparity, less than seven pre-natal visits, extended time from rupture of membranes until CS, emergency CS delivery, lack of appropriate antibiotic prophylaxis, increased surgical time, birth of twins, as well as excess vaginal manipulation (Olsen *et al.*, 2008; Farret *et al.*, 2015). HIV, severe anaemia and gestational diabetes are other co-morbidities which are also associated with elevated rates of puerperal infection, particularly SSIs (Diamond *et al.*, 1986). There was a significant association reported between hypertension, pre-eclampsia and wound infections, as women with these risk factors were three times more likely to develop wound infections (Dhar *et al.*, 2014).

No significant association between wound infections and parity has been demonstrated (Dhar *et al.*, 2014), although women who have already delivered more than six children were 1.4 times more likely to get an infection as opposed to women who were giving birth for the first time or had only one child. There is reduced penetration of antibiotics into the skin due to the avascularity of adipose tissue. Furthermore, the healing process is delayed as obesity provides greater mechanical stress on the wound (Vuolo, 2006).

A study by Dhar *et al.* (2014), found a significant association between premature rupture of membranes (PROM) and wound infections, with a four-fold increase. Frequent vaginal examinations may also contribute to an increased infection rate. The sterile amniotic fluid can possibly be infected if there are infections in the female genital area or the gastrointestinal tract. There is also an increased risk of chorioamnionitis as a result of PROM, which can be attributed to the loss of the protective effect conferred by the intact foetal membranes. The duration between the rupture of the membranes and surgical intervention also has an impact on the rate of wound infection. Once the membranes have ruptured, the sterility of the amniotic fluid is lost and can therefore serve as a transport medium, encouraging infection of any uterine and/or skin incisions (Gould, 2007).

Women with diabetes have been shown to be three to six times more likely to develop wound infections than women without diabetes (Nwankwo *et al.*, 2012; Dhar *et al.*, 2014). Fluctuating blood glucose levels increase the rate of infection and delays wound healing, by altering the ability of leukocytes to control the harmful proliferation of bacteria.

The advantageous effects of appropriate antibiotic prophylaxis in lowering the incidence of infection associated with CS are well recognised. Farret *et al.* (2015), reported that patients who were administered 2g of cefazolin intravenously prior to the operation had a 54% reduced the risk for any type of SSI. However, in a multivariate-adjusted odds ratio analysis, other variables such as extended time for ruptured membranes or the presence of comorbidities were shown to also affect the risk of infection. Nonetheless, the authors recommended that prophylaxis be administered to selected groups of patients undergoing CS (Farret *et al.*, 2015).

### **2.3 Deaths due to pregnancy-related sepsis – a cause for concern**

Maternal mortality is tracked by the Confidential Enquiry into Maternal Deaths Committee in South Africa (NCCEMD, 2016). The 6<sup>th</sup> report of this committee was issued in 2016. Non-pregnancy related infections, obstetric haemorrhage and hypertension were the top three main causes of maternal deaths, and accounted more than two-thirds of all maternal deaths. The largest category of maternal death was non-pregnancy related infections. However, maternal deaths from this cause had significantly decreased over time. Deaths from pregnancy-related sepsis (PRS) are defined as “those caused by infections of the genital tract associated with viable pregnancies.” There had been a decline in maternal deaths due to PRS between 2002 and

2012. The report indicated that 226 deaths from PRS were recorded in 2011-2013. Of these, 117 occurred after a normal vaginal birth, 88 after CS, 11 after CS complicated by bowel injury and 10 were attributed to chorioamnionitis. Out of the pregnancy-related sepsis causes, puerperal sepsis after normal vaginal delivery (NVD) accounted for 51.8% and puerperal sepsis after CS accounted for 38.9% of cases. Lack of appropriately trained medical practitioners was recorded as a significant factor in 24% of maternal deaths due to pregnancy-related sepsis (NCCEMD, 2016).

The Institutional Maternal Mortality Ratio (iMMR) attributed to PRS declined from 12.1 per 100 000 live births in 2002-2004 to 8.0 in 2011-2013. The iMMR causally related to the mode of delivery was three times higher for operative delivery, at 185.8 per 100 000 live births for CS compared to 66.6 per 100 000 live births for vaginal birth (NCCEMD, 2016).

There was a reduction from 4.1 per 100 000 live births in 2008-2010 to 3.1 in 2011-2013 with regard to the iMMR for deaths after Caesarean section (excluding cases of bowel injury). “Forty-three per cent of PRS deaths in 2011-2013 occurred at regional hospitals, and 30% occurred at district hospitals.” Limpopo, Mpumalanga and North-West were the three provinces with the highest iMMRs for PRS. While Gauteng and the Western Cape were among the two provinces with the lowest iMMRs for PRS. HIV status was known in 206 of the deceased women, of whom 137 (67%) were known to be living with HIV (NCCEMD, 2016).

It has been suggested that particular emphasis needs to be placed on developing new strategies for the management of high-risk patients and improving surgical practices to reduce the risk of extended LOS following CS (Blumenfeld *et al.*, 2015). Thus, prevention of such infections should be a healthcare priority in all countries. As infection continues to be a growing problem, there has also been a call for implementation of SSI surveillance during and after surgeries in order to attain a standardised measure of incidence (Gould, 2007; Dhar *et al.*, 2014).

## **2.4 HIV and the risk of sepsis**

Sub-Saharan Africa has been the area most affected by the HIV epidemic globally. High levels of HIV and the possible risk of dying due to complications of pregnancy have affected several women of child-bearing age in this region. There have been reports from clinicians practising in

high HIV prevalence settings that obstetric complications are common in women living with HIV. However, the supporting evidence is not clear (Verkuyt, 1995).

Sepsis is considered the most common complication yet the association between post-operative sepsis and the various variables implicated may not be so straightforward. For example, it seems plausible to expect an association between HIV infection and post-CS sepsis, however Rodriguez *et al.* (2001) demonstrated that there was no difference between post-operative morbidity among HIV-infected women undergoing CS and those in the control group. However, Moodliar *et al.* (2007) confirmed in a study carried out in a setting with high HIV prevalence rates that complications associated with CS are common, 14.2% of CS were associated with a complication. On the other hand, a systematic review which investigated the effects of pregnancy on HIV progression and survival did not find any clear evidence that pregnancy caused a rapid progression to an HIV-related illness or a drop in CD4 count to less than 200 cells per cubic millilitre (French and Brocklehurst, 1998).

A systematic review carried out by Calvert and Ronsmans (2013), to establish whether HIV-infected women are at increased risk of direct obstetric complications, found that studies including vaginal and CS deliveries have indicated that HIV-infected women had over three times the risk of puerperal sepsis compared with uninfected women. HIV-positive women were more susceptible to infections including puerperal sepsis after surgical procedures due to their immuno-compromised status and overall health compared to uninfected women (Graham and Hussein, 2003). It has been suggested that HIV-related thrombocytopenia, a condition in which there is a reduced platelet count in the blood, may lead to an increased risk of haemorrhage (Calvert and Ronsmans, 2013). Moreover, social factors like insufficient access to healthcare play a role in increasing a woman's risk of obstetric complications, and may be aggravated in HIV-infected women as a result of the discrimination and stigma faced by these women in certain settings (Calvert and Ronsmans, 2013).

An association between HIV and both uterine rupture and prolonged labour has been demonstrated (Calvert and Ronsmans, 2013). The higher risk of intrauterine infections associated with HIV is understandable, as the immunocompromised state related to HIV increases susceptibility to infections (Van Dillen *et al.*, 2010). The risk of experiencing postpartum infections may be increased by Caesarean sections. The authors indicated that the risk of intrauterine infections was higher among women who were HIV-infected and persisted among those undergoing CS deliveries. There is still uncertainty whether the increased risk of

endometritis and puerperal sepsis in the intra- and post-partum period is directly related to the pregnancy or indirectly linked to HIV or AIDS-associated infections (Calvert and Ronsmans, 2013).

There are limited studies conducted on the causes of death in pregnant or post-partum women by HIV status, with the exception of the South African Confidential Enquiries. In the 2011-2013 Confidential Enquiry report, 60.6% of women who died from pregnancy-related infections were HIV-positive, while 89% of maternal deaths attributed to non-pregnancy-related infections were in women living with HIV (NCCEMD, 2016).

In a study by Ferrero and Bentivoglio (2003) the various risk factors listed were: HIV infection associated factors (CD4+ lymphocyte count, mode of HIV acquisition, antiretroviral therapy during pregnancy), obstetrical factors (emergency CS, ruptured membranes, preterm delivery) and maternal factors (age, obesity, parity). Critically, in this study, HIV-infected women were shown to have an increased risk of postoperative morbidity regardless of whether or not a single dose of intravenous prophylactic antibiotic (generally a cephalosporin) was administered at the time of the CS (Ferrero and Bentivoglio, 2003). However, it must be noted that there are limited data on the complications among HIV-infected women undergoing CS delivery, but there appears to be a consistent finding of an increased complication rate when compared to HIV-uninfected women (Robinson *et al.*, 1987; Semprini *et al.*, 1995).

## **2.5 Antibiotic prophylaxis in Caesarean sections**

CS is one of the most common surgical procedures performed in medical practice worldwide. CS births are the most important known common factor that has been linked with post-partum bacterial infections, with a reported rate of wound infection between 1– and as much as 25% (Chaim *et al.*, 2000; Morisaki *et al.*, 2014; Henderson and Love, 1995). There is a 5–20 times greater risk of developing post-partum infections after CS delivery compared to vaginal delivery (Lamont *et al.*, 2011). Nonetheless, clear evidence points to a reduction in the risk of endometritis and other bacterial infections, even in low-risk (before labour and with intact membranes) pregnancies, when prophylactic antibiotics are utilised in CS (Smaill and Gyte, 2010). The application of universal prophylactic antibiotics in obstetrics has therefore been widely accepted in guidelines for several countries, such as the United States (US) and numerous Asian countries (Morisaki *et al.*, 2014). However, there are reports of barriers that

exist to providing effective antibiotic prophylaxis in all CS deliveries (Salim *et al.*, 2011). There are also continual discussions about the potential need for modifying prophylaxis regimens in particular high- or low-risk groups (Lamont *et al.*, 2011, Morisaki *et al.*, 2014). Based on studies in the US, there is an increased risk of bacterial infections in socially disadvantaged populations (Creanga *et al.*, 2012). In low-income settings, improving the safety and care provided when performing a CS can lead to improvements in maternal and neonatal outcomes, which is in keeping with the Millennium Development Goals and now the Sustainable Development Goals (United Nations, 2015b).

As noted, surgical site infections are a common complication of obstetric and gynaecological procedures, and so antimicrobials are commonly prescribed prophylactically, both pre-operatively and post-operatively, for procedures in Obstetrics and Gynaecology (Warnecke *et al.*, 1982). The judicious use of antibiotics can prevent post-partum infection of the mother and neonate and reduce the incidence of adverse drug reactions (Liu *et al.*, 2016). Indiscriminate use of antibiotics may result in the appearance of drug-resistant organisms (Smaill and Grivell, 2014). Antimicrobial usage in the above setting therefore becomes inevitable, but should be restricted in order to avoid excessive ecological pressure, leading to resistance. The rational use of antimicrobials in women of child-bearing age is important because it affects this population as well as their offspring.

In a study by Morisaki *et al.* (2014) the authors suggested that there may be a relation between the coverage of antibiotic prophylaxis in women having CS and the perception of the importance of guidelines and clinical audits in the facility. The authors further stated that even though obstetricians are seemingly aware of the increased risk of infection in most maternal complications when antibiotic prophylaxis is administered, there may also be a trend to overuse prophylaxis in scheduled CS deliveries as it is incorporated in the routine clinical protocol (Morisaki *et al.*, 2014).

Several studies have verified the efficacy of antibiotic prophylaxis in the reduction of post-CS infectious morbidity (Enkin *et al.*, 1989). Debates surrounding the duration of therapy and cost containment remain controversial. There is sufficient evidence of the need for and effectiveness of antibiotic prophylaxis in the prevention of SSIs. Hence the current debate places emphasis on the choice and timing of antimicrobial prophylaxis administration (Lamont *et al.*, 2011). Evidence-based guidelines recommend the use of prophylactic antibiotics before surgical incision. In order to be effective, a prophylactic agent only needs to be present at the time of

bacterial contamination (Ledger, 1986). As indicated in a study by Gonik and McGregor (1994), in women that have had a CS and presented with an infection post-CS, additional antibiotic therapy was only initiated after the diagnostic studies were completed if deemed necessary by the attending physician (Gonik and McGregor, 1994). An exception is made for CS delivery, where narrow-range antibiotics are administered after umbilical cord clamping due to putative neonatal benefit. However, recent evidence supports the use of pre-incision, broad-spectrum antibiotics, which result in a lower rate of maternal morbidity with no disadvantage to the neonate (Lamont *et al.*, 2011).

### ***2.5.1 Selection of prophylactic antibiotics***

In patients with known risk factors undergoing CS, infectious morbidity is reasonably common, this being in the form of post-partum endometritis, wound infection, or urinary-tract infection (Enkin *et al.*, 1989). *Ureaplasma* species (spp.), *Mycoplasma* spp., anaerobes or *Gardnerella vaginalis* are some of the common causative organisms responsible for polymicrobial bacterial vaginosis (Andrews *et al.*, 1995; Martens *et al.*, 1995; Watts *et al.*, 1990) and which can be isolated from the amniotic fluid and the chorioamnion during CS (Keski-Nisula *et al.*, 1997). There is a three- to eight-fold increased risk of endometritis and bacterial vaginosis should these causative organisms be detected post-CS (Andrews *et al.*, 1995; Watts *et al.*, 1990). Skin contaminants, as well as organisms responsible for bacterial vaginosis, make surgical wounds very susceptible to infection (Emmons *et al.*, 1988). The use of first-generation cephalosporins such as cefazolin provides good antibiotic activity against species of *Ureaplasma* and *Mycoplasma* (ACOG, 2003), but may lead to an increase in resistant anaerobic organisms (Newton and Wallace, 1998). Hence the rationale for adding other antimicrobial agents, such as metronidazole, clindamycin or azithromycin, is to provide a more extensive cover and particularly cover for anaerobes (Lamont *et al.*, 2011). The broad-spectrum antibiotics that have been evaluated are mainly single-agent extended-range penicillins, or second- or third-generation cephalosporins, but these have shown no advantage (Hopkins and Smaill, 2000).

Numerous studies have acknowledged the efficacy of a variety of regimens for antibiotic prophylaxis to reduce post-operative infectious morbidity. Although this general approach has led to significant reductions in the duration of hospitalisation (Duff, 1987), further attempts at cost containment have encouraged the recommendation to use less expensive (and less broad-



spectrum) antimicrobial agents and to reduce the number of peri-operative antibiotic doses (Faro *et al.*, 1990).

In a review by Cecatti (2005) it was found that, there was a homogenous protective effect in all women undergoing CS, despite the regimen used or study carried out. The author was thus persuaded of the need for all women undergoing CS to receive antibiotic prophylaxis in order to reduce the incidence of SSIs. Since there are similarities in the effectiveness of ampicillin and first generation cephalosporins, there is no justification for utilising agents with a broader spectrum or multiple antibiotics. However, there is still uncertainty, and a degree of variability in practice, with regard to optimal timing of administration and the number of doses.

### ***2.5.2 Duration and dosing of prophylactic antibiotics***

According to the current NDOH STG, the prophylactic dose in surgical prophylaxis is a single dose equal to the standard therapeutic dose. A second dose is only given if surgery is prolonged (NDOH, 2012). For all patients, intra-operative re-dosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the drug or there is excessive blood loss during the procedure (Bratzler *et al.*, 2013). Published guidelines and such as those from the American Society of Health-System Pharmacists (ASHP) have also been noted as recommending the use of cefazolin in CS (Bratzler *et al.*, 2013). According to the Zimbabwe Medicines Formulary and Treatment Guidelines 2011, women undergoing CS should receive a single dose of 1g ceftriaxone IV (Gidiri and Ziruma, 2014). Gidiri and Ziruma (2014) conducted a randomised clinical trial that compared the current Zimbabwean practice of repeated dose prophylactic antibiotics to a proposed single dose regime of prophylactic antibiotics for women undergoing CS. The authors concluded that whether a single dose of prophylaxis was given or a week's course of antibiotics, the regimens were equivalent in preventing infection and reported that there it was unnecessary to subject women to week-long antibiotics as this also increased nurses' workload. As these authors stated: "Clinicians have developed fears based on anecdotes of post-surgical infection and have gradually moved away from evidence-based regimens of antibiotic prophylaxis and adopted therapeutic regimens" (Gidiri and Ziruma, 2014). No added benefit of using multiple doses over single dose of antibiotics for prophylaxis of SSI has also been reported in previous studies (Shakya and Sharma, 2010; Slobogean *et al.*, 2010). It is therefore recommended that single

dose antibiotic prophylaxis be administered pre-operatively for emergency and elective CS. The 1998 Swedish and Norwegian consensus guidelines on the use of antibiotic prophylaxis in surgery also support this approach, which states that surgeons should be conservative when selecting antibiotics (Anonymous, 1998).

The cost implications with the use of antibiotics beyond the recommended time are important to consider, especially in resource-limited settings. A multiple-dose regime will necessarily be associated with higher cost compared to a single-dose regime, not just in terms of acquisition costs but also in terms of staff time. The use of a single-dose regime would be expected to reduce work load (Gidiri and Ziruma, 2014). The shortage of healthcare workers is a serious problem in many resource-limited settings. In addition, the effect on susceptibility patterns of the common bacteria causing SSIs should be considered.

By definition, the purpose of antimicrobial prophylaxis is to reduce bacterial colonisation and contamination at the time of surgery, and therefore allow the patient's immune system to overcome the threat of infection (Ledger, 1986; Kaimal *et al.*, 2008; Mangram *et al.*, 1999). Hence the prophylactic agent should be given empirically to ensure that adequate tissue concentrations are present during the time of CS. Since CS procedures very seldom exceed an hour, relatively short half-life agents should be efficacious (Gonik and McGregor, 1994).

Over the years, the administration of prophylactic antibiotics has become the responsibility of the anaesthesiologist. Therefore, there is a growing need for anaesthesiologists to understand the rationale behind antibiotic prophylaxis regimen choices (Dlamini *et al.*, 2015). In a study conducted by Dlamini *et al* (2015) the authors highlighted the importance of the timing of prophylaxis. It was found that the overall risk of postoperative infections, in particular endometritis, was significantly lower when prophylaxis was administered within one hour before skin incision compared to those who received prophylaxis after skin incision. To meet this timing, anaesthesiologists need to prescribe the prophylactic antibiotics in time, but also ensure their timeous administration (by themselves or by ward or theatre nurses).

### ***2.5.3 Timing of antibiotic prophylaxis***

The controversial issue of whether antibiotic prophylaxis for CS should be administered prior to the skin incision or at the time of the umbilical cord clamping remains. Conventionally, the

reason for delaying prophylaxis was to avoid masking a neonatal infection and to prevent an unnecessary septic workup. However, in recent studies there has been no increase in neonatal sepsis, sepsis investigations, or length of stay demonstrated with pre-incision administration (Costantine *et al.*, 2008). A meta-analysis published in 2008 by Constantine *et al.* supports antibiotic prophylaxis being administered prior to CS incision to reduce total infectious morbidity without adverse effects on neonatal outcomes. Despite current studies suggesting the possibility of more long-term effects of antibiotic prophylaxis on neonates, further long term follow up studies on neonates exposed to prophylactic antibiotics are still required (Dlamini *et al.*, 2015). As a result, in 2010, the American College of Obstetricians and Gynecologists suggested that antibiotic prophylaxis be administered within an hour before commencement of the surgery (ACOG., 2010). In the event of an emergency CS delivery, antibiotic prophylaxis should be initiated immediately (Dlamini *et al.*, 2015).

With respect to the timing of antimicrobial prophylaxis, the occurrence of errors has been reported by a multitude of investigators over the past decade. In a retrospective review of 2651 specified surgical procedures (aortic grafts, hip replacements, or colon resections) performed during 1993 at 44 hospitals, the Healthcare Quality Improvement Project of New York State reported that 27%–54% of all patients did not receive antimicrobial prophylaxis in a timely fashion (Silver *et al.*, 1996). Several countries, such as the United States, Netherlands, Spain, Israel, Canada, India, and Brazil, have produced a plethora of similar findings (Matuschka *et al.*, 1997). There have been various approaches to ensure optimal timing of prophylactic antibiotic administration and this aspect has been well investigated by healthcare epidemiologists.

Errors in antimicrobial prophylaxis are unlikely to generate a great deal of awareness, considering the increased expenditure on surgical site infections (Kirkland *et al.*, 1999). However, as there is strong evidence that lower rates of infection can be achieved with programmes to optimise antimicrobial prophylaxis, this problem deserves high priority (Burke, 2001). However, as is the case with all medical errors, a non-punitive approach is warranted. More emphasis on evaluating the root causes of such errors, rather than on the mistakes of individual surgeons, is needed (Burke, 2001).

## 2.6 Importance of stewardship plans and the threat of antibiotic overuse

“Antimicrobial stewardship acts at an organisational level and defines collective strategies to optimise antimicrobial prescribing through sustainable changes in practice”, as has been stated by Gottlieb and Nimmo (2011). Antimicrobial stewardship programmes are aimed at optimising the usage of antimicrobials to achieve the best clinical outcomes, while attempting to reduce adverse events and limit selective pressures that drive the emergence of resistance (SHEA, IDSA, PIDS, 2012). Therefore, all healthcare facilities should have antimicrobial stewardship programmes implemented in their institutions, as both a patient safety issue and a public health imperative (SHEA, IDSA, PIDS, 2012). The rising ineffectiveness of once-reliable antibiotics has forced many healthcare professionals to utilise alternatives that are much more toxic, more costly and less likely to be orally available, thus putting added pressure on an already highly strained hospital system. Also, when compared to susceptible bacteria, antibiotic-resistant organisms are associated with increased patient morbidity and mortality resulting in increased costs of healthcare (WHO, 2001; Gottlieb and Nimmo, 2011).

The introduction of antibiotics was one of the most significant developments in modern medicine. Their availability has helped in the treatment of increasingly complex care. The ability to control infections through the use of antimicrobial agents has had a major impact in all clinical areas, but particularly in surgery, transplantation medicine, oncology, and intensive care medicine. In 1945, penicillin resistance in *Staphylococcus aureus* was first discovered followed by the emergence of resistance to methicillin in 1961 (Barrett *et al.*, 1968). By 1999, methicillin resistance in *S. aureus* was found in more than 53% of isolates taken from patients in intensive care units in a US surveillance system (CDC, 2000).

While the emergence of antimicrobial resistance has been at the forefront, it has long been assumed that this issue would be addressed by the ongoing development of new compounds. However, over time there has been a decline in the development of new antibiotics, stressing that this approach cannot be relied upon (WHO, 2001; Gottlieb and Nimmo, 2011). Resistant infections not only result in increased morbidity and mortality but also noticeably increase healthcare costs (Boucher *et al.*, 2009; Lautenbach *et al.*, 2006). In order to control the emergence of resistant organisms, more comprehensive approaches will be required. Such approaches will need to ensure that adequate and appropriate therapeutic medicines are available, the availability of diagnostic tools to rapidly and reliably detect particular infection causing organisms as well as their antimicrobial susceptibilities are developed, and continuous

monitoring and promotion of vigorous infection control and antimicrobial stewardship programmes are in place (SHEA, IDSA, PIDS, 2012).

Agricultural practices, in which the use of antibiotics for prophylaxis and growth promotion is involved adds to the ecological pressure driving the emergence of resistance. As reported in numerous studies, a significant proportion of antibiotic use is unnecessary and the usage clearly varies between countries regardless of having similar clinical outcomes (WHO, 2001).

### ***2.6.1 Challenges to measuring antimicrobial use***

In order to address the issues that surround antibiotic use, it is important to measure the degree of antimicrobial resistance in community and healthcare-associated infections and outcomes of any interventions designed. There is currently a lot of variation in the systems used for data collection and collation between countries and there is limited coordination at an international level. It is of utmost importance to have a surveillance programme to measure antimicrobial resistance as well as to track antimicrobial utilisation (Gottlieb and Nimmo, 2011).

The provision of education to the public together with the various sectors (medical, veterinary and public health) is vital if appropriate use of antibiotics is to be achieved. However, education campaigns and guidelines alone are inadequate unless they are coupled with sustained interventions such as audit and feedback methods or a system in which proactive steps are taken to aid prescribing and having interventions that tackle poor performance (Dellit *et al.*, 2007; Gottlieb and Nimmo, 2011).

A number of countries have responded. For example, in 2011, the Australasian Society for Infectious Diseases and the Australian Society for Antimicrobials convened an Antimicrobial Resistance Summit. They proposed that educational initiatives needed to place more emphasis on the relevance of antimicrobial resistance to public health. They also emphasised that ASPs needed to be based on national guidelines and local epidemiology. They emphasised that ASPs needed to be implemented by a multidisciplinary team, ideally including infection prevention units, microbiologists, pharmacists and clinicians. This team needs strong support from senior hospital management and access to the necessary information technology. Other bodies have emphasised that the necessary procedures need to be in place to measure and monitor antimicrobial use at the institutional level, in order to enable internal benchmarking

(SHEA, IDSA, PIDS, 2012). ASPs should not be limited to healthcare facilities and should extend to community care and long-term care facilities. The creation of a well-resourced national body to govern educational activities and antibiotic stewardship programs would provide more control (Gottlieb and Nimmo, 2011).

EARS-Net (the European Antimicrobial Resistance Surveillance Network) and ESAC-Net (European Surveillance of Antimicrobial Consumption Network) are European networks which monitor surveillance systems nationally and are led by the European Centre for Disease Prevention and Control (ECDC) (ECDC, 2016). EARS-Net is responsible for documenting the prevalence and development of antibiotic resistance in Europe. The onus is upon each country to gather and collate their data and report it to a central database at ECDC annually. There should be careful interpretation when comparing resistance in European countries as the difference in sampling procedures may affect the results. Certain countries take blood cultures more often from patients whereas others may only focus on complicated cases. As a result, a distorted image of the resistance situation may be presented. ESAC-Net collects and analyses data on antimicrobial consumption in the community as well as the hospital sector. This data is then disseminated and used to provide feedback to European countries on indicators of antimicrobial consumption in order to monitor the progress towards the cautious use of antimicrobials (ECDC, 2016).

In Sweden, the foundation of STRAMA, a well-coordinated national strategy, was initiated due to the rapid emergence of resistance to penicillin among pneumococci. STRAMA has been critical to ensuring that measurement methods are of high quality and consistently applied. ResNet is a point prevalence measurement, which is representative of the time period in which the measurements were carried out. Due to the participation of all laboratories the design of ResNet is able to monitor resistance across the entire country. One particular challenge that this software presents is that aggregated data per laboratory for bacterial species and antibiotic are received and presented. As a result this does not allow the detection of the prevalence of multi-resistant strains. It is precisely this level of information that is needed for the development or updating of local treatment guidelines. Previously, such data could only be retrieved directly from each hospital's records. However, with complete coverage of all laboratories in Sweden, such data are now available to the relevant healthcare authorities, and can inform guideline development (Public Health Agency of Sweden, 2014).

### ***2.6.2 The need for specific measures in specific settings***

The implementation of effective regulatory controls is a vital aspect of reducing indiscriminate use of antibiotics and keeping levels of antimicrobial resistance low in both human and animal settings. The Australasian Society for Infectious Diseases and the Australian Society for Antimicrobials has highlighted the need for a comprehensive national antimicrobial resistance surveillance to monitor the extent of resistance present, in which bacteria and where (SHEA, IDSA, PIDS, 2012). Areas that should be monitored include medical (hospital and community) and veterinary areas, as well as agriculture (including imported food). There should be standardisation of methods used in resistance testing wherever possible to allow for comparison and pooling of data. An example is the standardisation of minimum inhibitory concentration breakpoints (Gottlieb and Nimmo, 2011).

Antibiotic usage surveillance is another area where additional focus is warranted. A comprehensive national monitoring and audit system focusing on all areas of antibiotic usage is essential. Approaches that have been suggested include comprehensive monitoring of the antibiotics used in all hospitals (where electronic systems are more likely to be present), sampling that is representative of community prescribing, and collection of distribution data from suppliers to the agricultural market. In addition, point-prevalence surveys are needed, in which the diagnosis is compared with the prescriptions issued. In order to ensure benchmarking and transparency, it has been recommended that hospitals voluntarily identify themselves in surveillance programmes (Gottlieb and Nimmo, 2011).

### ***2.6.3 The need for research on antimicrobial stewardship***

There are significant gaps in existing knowledge and understanding of antimicrobial resistance and the interventions that are effective in limiting both the emergence and the transmission of resistance. Research is required for the development of a more standardised explanation of both the appropriate and redundant overuse and abuse of antimicrobial therapy, as well as clear and unambiguous measures of such use (SHEA, IDSA, PIDS, 2012). Research is needed on patient-centred outcomes in order to determine the most effective and cost-efficient execution of interventions in various healthcare settings. Thus far, research has been hampered by poor study design and an absence of standardised definitions (SHEA, IDSA, PIDS, 2012). Research is also needed on the development and validation of clear and well-defined processes and measures

that can be used to assess the impact of antimicrobial stewardship interventions in facilities as well as across healthcare settings (SHEA, IDSA, PIDS, 2012).

#### ***2.6.4 The role of pharmacists in ASPs***

Pharmacists have been placed at the forefront of ASPs with responsibility for monitoring and controlling antibiotic use. As a means of saving on costs, the pharmacy department was typically the first to initiate one of many ASP-like interventions. Pharmacists are well suited for this task due to their role in processing medication orders and their expertise with the hospital formulary. Different hospital-based pharmacists may serve a range of roles in these programmes. Pharmacists in hospitals are able to notify prescribers when restricted items are prescribed and make them aware when authorisation is needed. Apart from being the custodians of medicines, they may also identify prescriptions which need to be reviewed by infectious diseases specialists and flag these prescriptions. However, due to the diverse responsibilities shouldered by pharmacists, there is rarely sufficient time allowed for a comprehensive review of antimicrobial therapy. In addition, not all pharmacists are equipped with adequate knowledge and training in infectious diseases to provide recommendations comfortably for complex cases. Thus, having a clinical pharmacist with specialised knowledge and training in infectious diseases working full or part-time on the administration of the ASP will be an added benefit (MacDougall and Polk, 2005).

Both pharmacists and professional nurses can be seen as existing resources that are more than capable of co-ordinating and implementing ASPs, as well as improving patient outcomes in both the in-patient and out-patient settings (Schellack *et al.*, 2016). It is essential in the South African context, where health human resources are scarce, to utilise these resources. Much of the attention to date has been placed on promoting optimal antimicrobial prescribing, and has thus been aimed predominantly at hospital-based medical practitioners. However, a comprehensive approach is needed, engaging all appropriate healthcare professionals. Nurses play an important role “in monitoring compliance with institutional guidelines and best practice, monitoring for drug allergies and side-effects, obtaining and reporting of therapeutic levels, management and administration of medicines with mixed dosages, e.g. insulin, and ensuring timely and correct administration of antimicrobials” (Schellack *et al.*, 2016). Through the integration of nurses in ASPs, there can be a shared sense of responsibility in the care of



patients. This also allows nurses increased professional autonomy, and corrects the misconception that ASPs are outside the scope of nursing responsibility and expertise.

Recently, Brink *et al.* (2016), have reported a significant decline (18.1%) in overall antibiotic usage as a result of interventions implemented by pharmacists, coupled with communication aimed at prescribers, in a South African private sector setting.

## **2.7 Medicine Use Evaluation as a concept**

A Medicines Use Evaluation (MUE) is “defined as an authorized, structured, ongoing review of prescribing, dispensing and use of medication” (Navarro, 2009). It is a continuous, methodical process that is designed to facilitate the appropriate and effective use of medications (Navarro, 2009). This process encompasses a review against predetermined criteria; followed by adequate changes to the treatment should these criteria not be met. There is constant monitoring of patients’ medication history before, during and after dispensing in order to achieve positive outcomes which will be beneficial to the patient. These evaluations can serve as a quality assurance measure to provide corrective action, prescriber feedback and further evaluations (AMCP, 2009).

MUE can be classified into three major categories (AMCP, 2009):

- *Prospective* – “evaluation of a patient's drug therapy before medication is dispensed”
- *Concurrent* – “ongoing monitoring of drug therapy during the course of treatment”
- *Retrospective* – “review of drug therapy after the patient has received the medication”

Each of these types is explored in some detail.

### **2.7.1 Prospective Review**

This method of evaluation enables the pharmacist to identify and resolve problems before the patient has received the medication and is practised routinely by pharmacists through the assessment of prescription medication dosages and directions for use, while providing a review of patient information for possible drug interactions or duplicate therapy (Navarro, 2009). Prospective review places responsibility on the healthcare provider to evaluate prescriptions and proactively identify and resolve potential medicine-patient problems. It therefore allows the

pharmacist the opportunity to interact with patients and communicate with members of the healthcare team to work on a treatment plan for each patient. Furthermore, in the community pharmacy and institutional settings, pharmacists will be able to determine the appropriateness of the prescribed medicines therapy as they will be able to assess the prescription order at the time of dispensing and use information from the patient's medical or pharmacy record. In the event that opportunities for improved patient care are identified, the pharmacist can contact the prescriber to discuss alternative treatment options (Navarro, 2009).

High quality data can be obtained with strong validity. However, prospective review can be expensive, as the process is time-consuming to design and implement (Kalogeropoulos, 2014).

### ***2.7.2 Concurrent review***

In concurrent review, the review is conducted during the course of treatment, as it presents pharmacists with the opportunity to notify prescribers of the potential problems and intervene in areas such as drug-drug interactions, duplicate therapy, over- or under-utilisation and excessive or insufficient dosing. Concurrent review enables the patient's treatment plan to be modified in real time, if necessary. In an era of electronic prescribing, this process enables pharmacists to make interventions prior to the medicine being dispensed. It is vital that pharmacists have access to complete and current medicines and allergy records for the patient, in addition to adequate knowledge of appropriate therapeutic interchanges for patients. Healthcare practitioners are able to offer education on the proper use of medications and determine if there are specific patient needs that need to be addressed through adequate patient counseling (Navarro, 2009).

### ***2.7.3 Retrospective Review***

A retrospective review enables pharmacists to identify patterns in prescribing, dispensing or administering medicines. As a measure to avoid a repetition of inappropriate medication use, prospective standards and target interventions can be developed by monitoring current patterns of medication use. It is a relatively inexpensive process, as results and data can be quickly generated. However there is a risk for potential bias as there can be missing data and unmeasured confounders (Kalogeropoulos, 2014). Retrospective review may aid prescribers in improving the care of their patients, either individually or within a certain target population (Navarro, 2009).

#### ***2.7.4 The importance of MUE***

MUE programmes play a major role in helping healthcare systems “understand, interpret, evaluate and improve the prescribing, administration and use of medicines” (AMCP, 2009). In particular, they appeal to funders as they can be used to foster more efficient use of limited healthcare resources. Pharmacists are able to contribute to MUEs due to their knowledge and expertise in the management of medicines therapy. MUEs also encourage a multi-disciplinary team approach to the care of patients (AMCP, 2009).

According to the WHO, the most important aim of medicines utilisation research is to contribute to the rational use of medicines in populations. Without having knowledge of the prescribing patterns of medicines used, it is difficult to initiate a discussion on rational medicines use or to suggest measures to improve prescribing habits. The supply of information on the past performance of prescribers is essential to any auditing system. Medicines utilisation research alone cannot provide answers, but it can significantly assist in the rational use of medicines (WHO, 2003). Pharmacists participating in medicines utilisation research, such as MUEs, can have a direct impact on improving the quality of care for patients individually and as populations (AMCP, 2009).

#### ***2.7.5 Monitoring antibiotic prophylaxis using a retrospective MUE***

Retrospective MUE evaluates therapy after the patient has received the medication with the aim of detecting patterns in prescribing, dispensing or administering of medicines. Some of the common issues that such a programme can address are: appropriate generic use, clinical abuse/misuse, drug-disease contraindications, drug-drug interactions, inappropriate duration of treatment, incorrect dosage, use of on-formulary (essential medicines list) medications whenever appropriate, over- and under-utilisation, therapeutic appropriateness and/or duplication. For the purpose of monitoring current patterns of antimicrobial prophylaxis use, prospective standards can be used to detect inappropriate medication use and therefore target interventions to prevent recurrence. The outcomes of such an evaluation may aid prescribers in improving medicines use and patient care by initiating corrective action (AMCP, 2009).

As the development and use of MUEs continues, a more multidisciplinary approach involving a range of healthcare professionals will be needed in order to move closer to the ideal of comprehensive healthcare utilisation evaluation (AMCP, 2009; Navarro, 2009).

## 2.8 Theoretical framework

This research is located within the theoretical framework of Pharmaceutical Care, as elucidated by Hepler and Strand (1990). Pharmaceutical care was defined by Hepler and Strand as the "responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life." At the time of the development of the concept, Hepler and Strand pointed to the high burden posed by adverse drug reactions (ADRs). They noted that, in 1987, an estimated 12 000 deaths and 15 000 hospitalizations were reported to the FDA as a result of ADRs. They therefore emphasised the social responsibility of the pharmacy profession in reducing preventable drug-related morbidity and mortality, reducing the number of ADRs, the length of hospital stays, and ultimately the cost of care. At the time, they called for new practice standards, but also the need to establish mutual relationships with other health-care professions. The patient outcomes that pharmacists seek to achieve are (1) cure of a patient's disease, (2) elimination or reduction of a patient's symptomatology, (3) arresting or slowing of a disease process, or (4) prevention of a disease or symptomatology. In order to achieve these, pharmacists are enjoined to (1) identify potential and actual medication-related problems, (2) resolve actual medication-related problems, and (3) prevent potential medication-related problems.

Hepler and Strand identified the following categories of medication-related problems:

- "Untreated indications. The patient has a medical problem that requires medication therapy (an indication for medication use) but is not receiving a medication for that indication.
- Improper drug selection. The patient has a medication indication but is taking the wrong medication.
- Sub therapeutic dosage. The patient has a medical problem that is being treated with too little of the correct medication.
- Failure to receive medication. The patient has a medical problem that is the result of not receiving a medication (e.g., for pharmaceutical, psychological, sociological, or economic reasons).
- Over dosage. The patient has a medical problem that is being treated with too much of the correct medication (toxicity).
- Adverse drug reactions. The patient has a medical problem that is the result of an adverse drug reaction or adverse effect.
- Drug interactions. The patient has a medical problem that is the result of a drug–drug, drug–food, or drug–laboratory test interaction.

- Medication use without indication. The patient is taking a medication for no medically valid indication.” (Hepler and Strand, 1990).

In unpacking the demands of this model of professional action, the American Society of Hospital Pharmacists stated: “In the provision of pharmaceutical care, pharmacists use their unique perspective and knowledge of medication therapy to evaluate patients’ actual and potential medication-related problems. To do this, they require direct access to clinical information about individual patients. They make judgments regarding medication use and then advocate optimal medication use for individual patients in cooperation with other professionals and in consideration of their unique professional knowledge and evaluations. Pharmaceutical care includes the active participation of the patient (and designated caregivers such as family members) in matters pertinent to medication use” (ASHP, 1993).

The overlaps with the standards and processes that inform ASPs are clear and obvious. This study was located within that tradition, and drew upon the theoretical underpinning of the concept of pharmaceutical care. The purpose of this retrospective action research was to bring forth action and knowledge that will be beneficial to the patients’ health as well the healthcare sector in general coupled with contributing to the rational and responsible use of medicines, in particular antibiotics, through the application of medicines use evaluation.

## **2.9 Summary**

CS remains an important risk factor for post-partum infection in many health facilities. As there is no consistent protocol for the provision of prophylactic antibiotics for CS in Heidelberg Hospital, the findings of this study will help to improve the quality of patient care by using a standard protocol for antibiotic prophylaxis as stipulated by the National Department of Health or provide evidence for the reconsideration of that protocol.

This chapter comprised of a literature study which covered the key issues pertaining to antibiotic prophylaxis in CS. This in turn provided an overall view of important parameters to be considered when prophylaxis is administered, taking into account the risk of post-operative infections as well as the rising rates of HIV and its association to complications associated with CS. It also highlighted the importance of antimicrobial stewardship in facilities and the consequences of antibiotic overuse.

## **CHAPTER III: METHODS**

### **3.1 Introduction**

Chapter 3 provides an overview of the methods used in the study. It highlights the study design used as well as the target population and study sample. It also highlights the methods used in the collection of the quantitative and qualitative data, considers the potential for bias and how that was managed, and the limitations that were expected and how those were avoided. This chapter also describes the ethical approval steps that were required prior to data collection.

### **3.2 Study design**

A mixed design study was conducted with a quantitative phase as well as a qualitative phase. The quantitative phase involved a descriptive observational study design.

### **3.3 Target population and study sample**

#### ***3.3.1 population Target***

The setting for the study was the maternity ward at Heidelberg Hospital, where women undergoing Caesarean sections (CS) were treated and where records of their management were kept. The population of interest for this study was females undergoing CS deliveries.

#### ***3.3.2 Selection of study population***

The population that was used for the study consisted of patients who were admitted to Heidelberg Hospital for CS during a selected 3 month period (April, May, and June 2016) and who met the following inclusion criteria:

- healthy females (adolescents and adults) undergoing CS; and
- receiving antibiotic prophylaxis associated with CS.

In addition, data on patients' HIV status, age and parity was recorded.

Patients whose records showed vaginal delivery were not considered for the study.

### **3.3.3 Sample size considerations**

For the purpose of this study, a census approach was used. The total number of CS cases (elective and non-elective) during the selected 3 month period was estimated to be about 120 subjects. This was large enough to allow for detailed information about sub-groups within the population to be gathered from hospital records. A census approach also avoided sampling bias.

The method of sampling for the qualitative component, which was aimed at obtaining potential reasons for non-compliance from the medical staff, was expert sampling. This was essentially a specific sub-case of purposive sampling and was the best way to elicit the views of the medical staff that have specific expertise.

### **3.4 Collection of interview data (Qualitative phase)**

The qualitative phase involved structured interviews (see Appendix 1) with medical staff to establish reasons for any non-compliance which was detected. A total of 7 medical officers were approached to participate in the interviews. The medical officers were briefed on the purpose of the study, methods used to meet this purpose as well as the benefits of the study and thereafter were required to sign an information sheet and informed consent to participate in the research (see Appendix 2) before the interview could begin. Individual interviews with an estimated length of half an hour were used. Medical officers were asked a series of questions regarding their experiences and the use of antibiotic prophylaxis in patients undergoing Caesarean sections in the maternity ward at Heidelberg Hospital. Participants were not obliged to answer the questions if they felt uncomfortable and were also free to withdraw their consent to participate at any time. There was no need for translation since all doctors were fluent in English and used this as their preferred language of communication during the interview.

### **3.5 Collection of exposure data (Quantitative phase)**

A Medicine Use Evaluation data capture sheet (see Appendix 3) was used to extract data from the prescriptions and health records for patients who met the inclusion criteria in each of the three months under review. Data were recorded on the following elements:

- demographics (age, ethnicity, parity, HIV status (if known));
- reason for the Caesarean section;
- factors that required treatment with antibiotics post-operatively;

- antibiotic name;
- dose;
- route of administration;
- frequency of administration and;
- duration of treatment.

Trends in the utilisation of specific antimicrobial medicines, their doses and durations of use were established.

The medicines utilisation evaluation (MUE) data collection process was carried out in a series of steps:

Step 1: Established responsibility - the Pharmacy and Therapeutics Committee was informed of the study as this included members with specific expertise. This step also created a demand for the information gathered and improved the chances of implementation of proposed remedial actions.

Step 2: Developed scope of activities - emphasis was placed on the most frequently used antimicrobials for surgical prophylaxis and on the cost implications of potential non-compliance.

Step 3: Established criteria (guidelines) - defined correct medicines use and thresholds according to the appropriate medicine for the target condition, correct dose, duration, contraindication, drug-drug interactions and outcome. The criteria were formulated by the researcher and thresholds were set as targets, based on value judgements by the researcher.

Step 4: Collected data through retrospective evaluation - data were extracted from inpatient prescription forms and patient records. Due to the absence of electronic databases, data were extracted from patient records manually. Average medicine cost was calculated using the cost per unit for each antimicrobial given intravenously or orally, using the prevailing tender price as charged to the facility by the Gauteng provincial depot.

Step 5: Analysed data by tabulating results for each indicator and analysed to see if criteria are met and threshold was met - attempts to determine why thresholds or benchmarks are not met were made, using expert interviews with medical staff.

Step 6: Developed recommendations to address inappropriate drug use and methods to resolve any drug use problem - this is the step where corrective action was implemented after having structured interviews with the prescribers so that action was targeted to areas of concern such as prescribing patterns, medication misadventures, and quality of medicines therapy or economic considerations.



Step 7: Assessed the effectiveness of the MUE programme - evaluation of the outcomes was done and reasons for positive and negative results were documented. Before implementing appropriate changes, continued observation will be undertaken.

In order to measure existing practice against a defined standard, the following criteria were established, based on the current National Department of Health Standard Treatment Guidelines/Essential Medicines List for Adult Hospital care (NDOH, 2012). It was acknowledged that these criteria did not represent the locally-developed and implemented practices, but the differences were explored in the qualitative phase. The thresholds were set by the researcher, based on the current guidelines and expected compliance.

Criteria (Guidelines)		Threshold
■	<b>Indication</b>	
➤	Surgical prophylaxis	90%
➤	<i>Staphylococci</i> and most <i>Streptococci</i> infections	
■	<b>Dose</b>	
➤	Surgical prophylaxis: 1g at induction, repeated 4 hourly during prolonged surgery	
➤	<i>Staphylococci</i> and most <i>Streptococci</i> infections: IM or IV, 0.5-1g 6-12 hourly; max 6g/day	95%
➤	renal impairment : dose adjustment as follows:	
•	eGFR* 10-50ml/min, 100% of dose 12 hourly	
•	eGFR*< 10ml/min, 50% of dose 24-48 hourly	
■	<b>Duration</b>	
➤	Surgical prophylaxis: single dose	95%
➤	<i>Staphylococci</i> and most <i>Streptococci</i> infections: 5-7 days	
■	<b>Contraindications</b>	
➤	Previous severe immediate-type hypersensitivity to any penicillin or cephalosporin	100%
■	<b>Drug interactions - To be used with caution:</b>	
➤	Warfarin, NSAIDs, oral contraception, probenecid	90%
■	<b>Outcome</b>	
➤	No initiation of a therapeutic course of antibiotics post-delivery	90%
➤	Negative cultures	
➤	No septicemia	

**Table 3.1: MUE Criteria for cefazolin use in surgical prophylaxis in CS**

\*eGFR – estimated glomerular filtration rate (as estimated using standard methods)

### **3.6 Bias and limitations**

The assumption made regarding this study was that it was intended to deliberately change prescribing practices among prescribers. It was also difficult to get sufficient time with medical practitioners to extract useful information regarding their reasons for non-compliance. Some were reluctant to share the reasons for their choices. A non-punitive approach was used, with the opportunity to strengthen national guidelines emphasised. Time was a limitation in this study; since the data was collected retrospectively, information could only be obtained once CS have been done and the time available to extract data was limited. A contributing factor was getting approval from the Gauteng Department of Health, which was very time consuming and resulted in a delay in the data collection process. Since Heidelberg Hospital is a primary level hospital that does not admit a large number of patients, acquiring an adequate sample size was yet another limitation.

### **3.7 Statistical analysis**

At the end of the 3 month period, data were captured from the Medicine Use Evaluation data capture sheet onto MS Excel spreadsheets and subjected to descriptive statistical analysis. The quantitative data values were represented in a frequency distribution tables by grouping them into categories (e.g., age, parity), and thereafter depicted in a frequency distribution bar charts. Measures of central tendency were also used (mean, median) as well as measures of dispersion. The average treatment cost per patient was calculated and compared to the cost of a single dose regimen to highlight the impact on expenditure.

The qualitative data were thematically coded, grouped and then analysed. These codes used are represented in a table (see Appendix 4). Qualitative data, in the form of interview transcripts, were examined for themes that described and explained the reasons for antibiotic prophylaxis choices at Heidelberg Hospital. The transcripts were also examined for evidence to justify any alternative protocols being used.

### **3.8 Ethics**

Prior permission for the study was sought from the clinical manager of Heidelberg Hospital (see Appendix 5) as well as conditional approval being granted from the Gauteng Department of Health Research Committee (see Appendix 6). Individual patients' written informed consent for the data extraction was not needed, as only anonymised, retrospective data were utilised. Nonetheless, final ethical approval was obtained from the Biomedical Research Ethics Committee of the Faculty of Health Sciences, University of KwaZulu-Natal (BREC reference number: BE508/15) (see Appendix 7). There were no incentives involved for information obtained from the medical staff. The study had no sponsors or funding necessary since no money was required to extract information from the prescriptions and patient records.

## **CHAPTER IV: RESULTS**

### **4.1 Introduction**

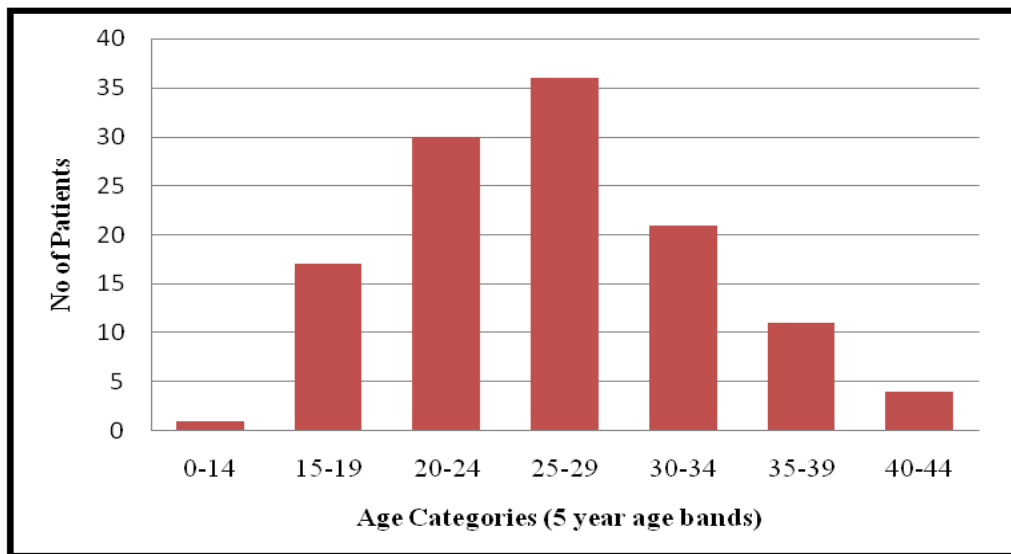
This chapter presents an analysis of the quantitative and qualitative data from the study. All data were collected at Heidelberg Hospital and are only representative of the 3 month study period. The raw data were extracted from the Medicine Use Evaluation capture sheet and were displayed using frequency tables and graphs. Quantitative data such as patient demographic data were analysed in terms of descriptive statistics. The gravidity and HIV status of the patients was also taken into account. The factors that prompted antibiotic use in post-operative CS patients were highlighted in order to examine whether prolonged antibiotic use was justified. The indication for the CS performed was also presented as well as the duration of treatment received. The qualitative aspect of the study presents data collected through interviews with the medical officers and describes their views and opinions regarding antibiotic prophylaxis and post-operative management.

### **4.2 Medicine Use Evaluation**

#### ***4.2.1 Patient demographic data***

The records for 120 patients who underwent CS during April, May, and June 2016 were examined retrospectively. The patients in the sample had a median age of 26 years (interquartile range (IQR): 22-31 years). Most women who delivered fell into the 20-24 and 25-29 years age categories as can be seen in Figure 4.1 below.

**Figure 4.1: Age distribution of women undergoing CS delivery**



#### ***4.2.2 Gravidity and HIV status***

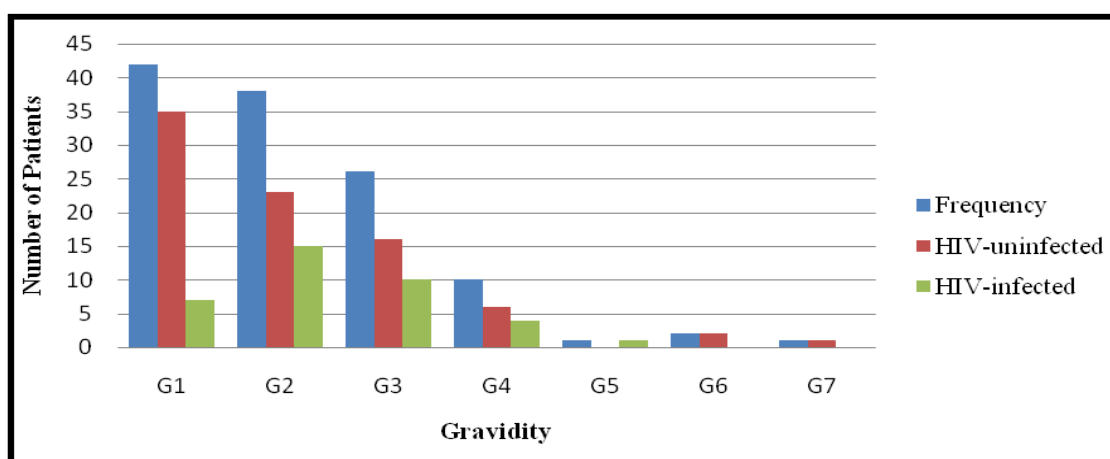
Of the 120 patients who delivered by CS, 83 (69.2%) tested negative for HIV. As seen in Table 4.1, 42 patients (35.0%) were delivering for the first time (Gravida 1), of which the majority (35 women; 83.3%) were HIV-uninfected. A higher percentage of Gravida 2 patients (15/38, 39.5%) tested positive for HIV. Of those delivering for the third time (G3), 38.5% (10/26) were recorded to be living with HIV. The percentage of HIV-uninfected and HIV-infected women is shown per gravidity status.

GRAVIDITY	FREQUENCY	HIV-uninfected	HIV-infected
	n (%)	n (%)	n (%)
G1	42 (35.0)	35 (83.3)	7 (16.7)
G2	38 (31.7)	23 (60.5)	15 (39.5)
G3	26 (21.7)	16 (61.5)	10 (38.5)
G4	10 (8.3)	6 (60.0)	4 (40)
G5	1 (0.8)	0 (0)	1 (100)
G6	2 (1.7)	2 (100)	0 (0)
G7	1 (0.8)	1 (100)	0 (0)
TOTAL	120 (100)	83 (69.2)	37 (30.8)

**Table 4.1: Gravidity and HIV status**

The distribution of gravidity and HIV status is illustrated in Figure 4.2..

**Figure 4.2: Distribution of gravidity and HIV status (N=120)**



#### 4.2.3 Indications for Caesarean section

As CS is not offered on an elective basis in the public sector, the indications for a CS generally represent a complication with the pregnancy. Table 4.2 shows the distribution of indications for

a CS, stratified by HIV status. As can be seen, in two pregnancies (1 of which was in an HIV-infected mother), an apparently elective CS was performed. The three most common indications for a CS were a prior CS (34/120, 28.3%), foetal distress (27/120, 22.5%) and cephalopelvic disproportion (27/120, 22.5%). The percentage of HIV-uninfected and HIV-infected women is shown per CS indication.



Complications	Frequency	HIV-uninfected	HIV-infected
	n (%)	n (%)	n (%)
Previous CS	34 (28.3)	19 (55.9)	15 (44.1)
Foetal distress	27 (22.5)	19 (70.4)	8 (29.6)
Cephalopelvic disproportion (CPD)	27 (22.5)	22 (81.5)	5 (18.5)
Breech position	7 (5.8)	4 (57.1)	3 (42.9)
Slow progress / prolonged labour	6 (5.0)	3 (50.0)	3 (50.0)
Foetal distress & cephalopelvic disproportion (CPD)	5 (4.2)	3 (60.0)	2 (40.0)
Pregnancy-induced hypertension (PIH)	2 (1.7)	2 (100)	0 (0)
Failed induction	2 (1.7)	2 (100)	0 (0)
Premature rupture of membranes (PROM)	2 (1.7)	2 (100)	0 (0)
Twins	2 (1.7)	2 (100)	0 (0)
Meconium stained liquor (MSL)	2 (1.7)	2 (100)	0 (0)
Vaginal warts	1 (0.8)	1 (100)	0 (0)
Grand parity	1 (0.8)	1 (100)	0 (0)
Apparently elective-no complication recorded	2 (1.7)	1 (50.0)	1 (50.0)
<b>TOTAL</b>	<b>120</b>	<b>83 (69.2)</b>	<b>37 (30.8)</b>

**Table 4.2: Indications for Caesarean section**

#### ***4.2.4 Recorded reasons for extended antibiotic regimens***

Although the NDOH STG recommends that only a single dose of cefazolin be administered, pre-operatively, for any pelvic surgery not exceeding 4 hours' duration, none of the 120 patients

received this regimen. Instead, one of two regimens was used during the in-patient stay: 1 day of IV cefazolin, administered every 8 hours (83/120, 69.2%) or 3 days' of IV cefazolin administered every 8 hours (37/120, 30.8%).

It was striking that every HIV-uninfected women (83/120, 69.2%) received 3 doses (1 day) of cefazolin IV, whereas every women who was recorded as HIV-infected received 9 doses (3 days' therapy) of cefazolin IV and metronidazole IV. As is shown in Table 4.3, this was true across every category of gravidity.

<b>GRAVIDITY</b>	<b>HIV-uninfected n (%)</b>	<b>HIV-infected n (%)</b>	<b>1 day cefazolin IV n (%)</b>	<b>3 days' cefazolin IV + metronidazole IV n (%)</b>
<b>G1</b>	<b>35 (83.3)</b>	<b>7 (16.7)</b>	<b>35 (83.3)</b>	<b>7 (16.7)</b>
<b>G2</b>	<b>23 (60.5)</b>	<b>15 (39.5)</b>	<b>23 (60.5)</b>	<b>15 (39.5)</b>
<b>G3</b>	<b>16 (61.5)</b>	<b>10 (38.5)</b>	<b>16 (61.5)</b>	<b>10 (38.5)</b>
<b>G4</b>	<b>6 (60.0)</b>	<b>4 (40)</b>	<b>6 (60.0)</b>	<b>4 (40)</b>
<b>G5</b>	<b>0 (0)</b>	<b>1 (100)</b>	<b>0 (0)</b>	<b>1 (100)</b>
<b>G6</b>	<b>2 (100)</b>	<b>0 (0)</b>	<b>2 (100)</b>	<b>0 (0)</b>
<b>G7</b>	<b>1 (100)</b>	<b>0 (0)</b>	<b>1 (100)</b>	<b>0 (0)</b>
<b>TOTAL</b>	<b>83 (69.2)</b>	<b>37 (30.8)</b>	<b>83 (69.2)</b>	<b>37 (30.8)</b>

**Table 4.3: Distribution of gravidity, HIV status and duration of IV antibiotics**

Although still in draft form, the widely-distributed Guidelines for Maternity Care in South Africa (Department of Health, 2016) have provided a list of conditions where therapeutic rather than prophylactic antibiotics are indicated:

- severe immunocompromise (e.g. history of recent AIDS defining illness or CD4+ cell count<250 cells/mL);
- evidence of chorioamnionitis (including offensive liquor);
- prolonged labour with many per vaginal examinations after rupture of membranes;
- obstructed labour (usually with systemic signs of sepsis); and

- CS delivery following failed vacuum extraction

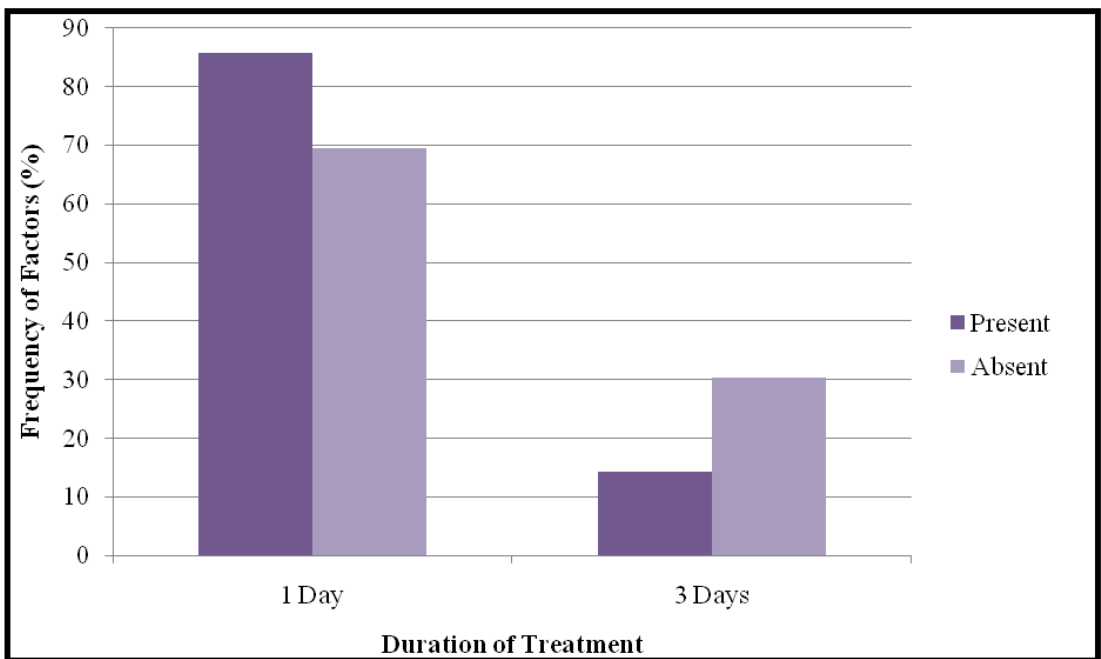
Once this draft became available, an attempt was made to track whether the clinical notes indicated application of these principles. However, for 11/120 cases (9.2%), the original notes could not be retrieved again. However, in every case, previous data extraction had recorded HIV status and the duration of IV antibiotics. As shown in Table 4.4, 102/120 patients (85.0%) did not have a reason from this list recorded as justification for a full therapeutic course rather than a prophylactic course. However, the link between HIV status and duration remained as invariable as before. In each of the 7/120 (5.8%) cases in which a discernible cause for the prolonged antibiotic course was recorded, this was based on prolonged labour with many per vaginal examinations after rupture of membranes. Nonetheless, 6/7 of these patients received only 3 doses of cefazolin IV. Only one patient was readmitted during the study period for sepsis and was treated accordingly with antibiotics. As shown in Table 4.4, in addition to the IV cefazolin administered in the ward, each HIV-infected patient also received metronidazole 500mg IV, for the same period (3 days).

<b>Presence of risk factors</b>	<b>Frequency N (%)</b>	<b>HIV-uninfected n (%)</b>	<b>HIV-infected n (%)</b>	<b>1 day cefazolin IV n (%)</b>	<b>3 days' cefazolin IV + metronidazole IV n (%)</b>
<b>Present</b>	<b>7 (5.8)</b>	<b>6 (85.7)</b>	<b>1 (14.3)</b>	<b>6 (85.7)</b>	<b>1 (14.3)</b>
<b>Absent</b>	<b>102 (85.0)</b>	<b>71 (69.6)</b>	<b>31 (30.4)</b>	<b>71 (69.6)</b>	<b>31 (30.4)</b>
<b>File not found</b>	<b>11 (9.2)</b>	<b>6 (54.5)</b>	<b>5 (45.5)</b>	<b>6 (54.5)</b>	<b>5 (45.5)</b>
<b>TOTAL</b>	<b>120</b>	<b>83 (69.2)</b>	<b>37 (30.8)</b>	<b>83 (69.2)</b>	<b>37 (30.8)</b>

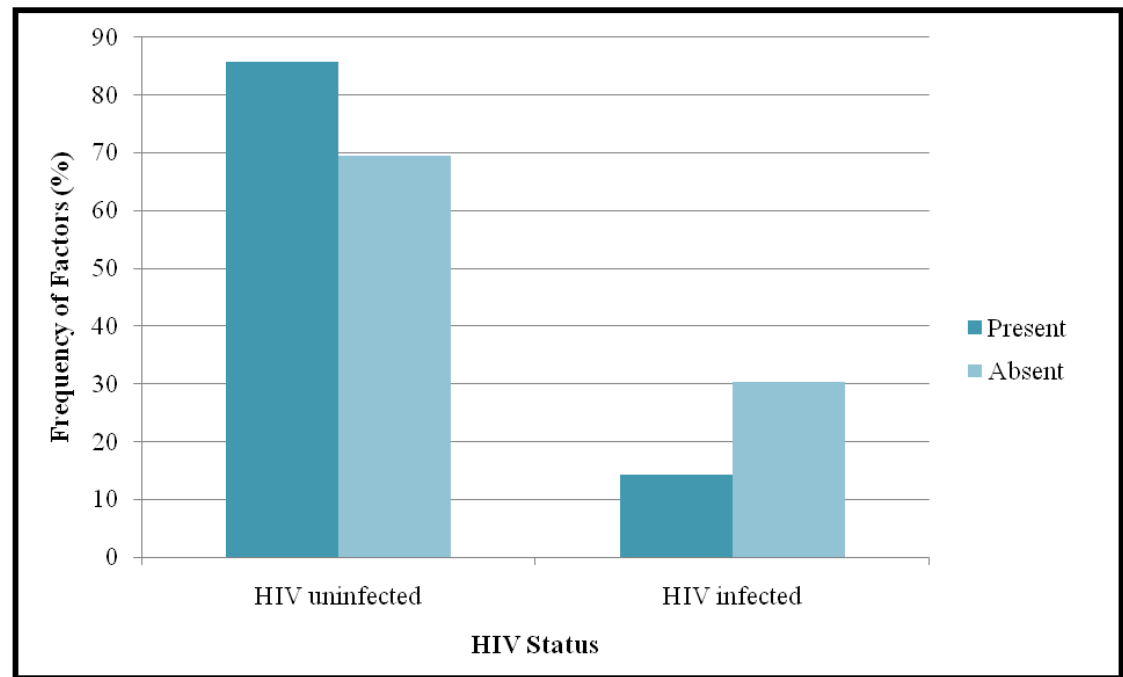
**Table 4.4: Factors requiring prolonged (therapeutic) antibiotics**

As seen in Figures 4.3 and 4.4 below, the duration of treatment in the presence or absence of factors requiring antibiotics corresponded only with the HIV status of the patients, and not with the presence or absence of discernible factors for prolonged, therapeutic courses of antibiotics.

**Figure 4.3: Distribution of patients and duration of treatment received, by presence or absence of discernible indications for prolonged antibiotics (N=109)**



**Figure 4.4: Distribution of HIV status and presence or absence of discernible indications for prolonged antibiotics (N=109)**



When the indications for CS were compared with the recorded reasons for CS, some of which also included reasons that overlapped with those stipulated in the draft Guidelines for Maternity Care in South Africa (Department of Health, 2016) for a therapeutic rather than prophylactic course of antibiotics, the connection with regard to HIV status and treatment was maintained, without exception, as seen in Table 4.5 below.

<b>Complications</b>	<b>HIV- uninfected  n (%)</b>	<b>HIV- infected  n (%)</b>	<b>1 day cefazolin IV  n (%)</b>	<b>3 days' cefazolin IV + metronid -azole IV  n (%)</b>
<b>Previous CS</b>	<b>19 (55.9)</b>	<b>15 (44.1)</b>	<b>19 (55.9)</b>	<b>15 (44.1)</b>
<b>Foetal distress</b>	<b>19 (70.4)</b>	<b>8 (29.6)</b>	<b>19 (70.4)</b>	<b>8 (29.6)</b>
<b>Cephalopelvic disproportion (CPD)</b>	<b>22 (81.5)</b>	<b>5 (18.5)</b>	<b>22 (81.5)</b>	<b>5 (18.5)</b>
<b>Breech position</b>	<b>4 (57.1)</b>	<b>3 (42.9)</b>	<b>4 (57.1)</b>	<b>3 (42.9)</b>
<b>Slow progress / prolonged labour</b>	<b>3 (50.0)</b>	<b>3 (50.0)</b>	<b>3 (50.0)</b>	<b>3 (50.0)</b>
<b>Foetal distress &amp; cephalopelvic disproportion (CPD)</b>	<b>3 (60.0)</b>	<b>2 (40.0)</b>	<b>3 (60.0)</b>	<b>2 (40.0)</b>
<b>Pregnancy-induced hypertension (PIH)</b>	<b>2 (100)</b>	<b>0 (0)</b>	<b>2 (100)</b>	<b>0 (0)</b>
<b>Failed induction</b>	<b>2 (100)</b>	<b>0 (0)</b>	<b>2 (100)</b>	<b>0 (0)</b>
<b>Premature rupture of membranes (PROM)</b>	<b>2 (100)</b>	<b>0 (0)</b>	<b>2 (100)</b>	<b>0 (0)</b>
<b>Twins</b>	<b>2 (100)</b>	<b>0 (0)</b>	<b>2 (100)</b>	<b>0 (0)</b>
<b>Meconium stained liquor (MSL)</b>	<b>2 (100)</b>	<b>0 (0)</b>	<b>2 (100)</b>	<b>0 (0)</b>
<b>Vaginal warts</b>	<b>1 (100)</b>	<b>0 (0)</b>	<b>1 (100)</b>	<b>0 (0)</b>
<b>Grand parity</b>	<b>1 (100)</b>	<b>0 (0)</b>	<b>1 (100)</b>	<b>0 (0)</b>
<b>Apparently elective – no complication recorded</b>	<b>1 (50.0)</b>	<b>1 (50.0)</b>	<b>1 (50.0)</b>	<b>1 (50.0)</b>
<b>TOTAL</b>	<b>83</b>	<b>37</b>	<b>83</b>	<b>37</b>

**Table 4.5: Indications for Caesarean sections and duration of treatment**

As shown in Table 4.5, a combination of medicines was administered for HIV-infected patients. Then, regardless of HIV status, every patient was issued on discharge with a prescription for oral amoxicillin 500mg 15 (500mg every 8 hours for 5 days) and oral metronidazole 400mg 21

(400mg every 8 hours for 5 days). Those who were HIV-negative therefore received at least 6 days of continuous antibiotics, and those who were HIV-positive received at least 8 days of continuous antibiotics, in each case a combination of a beta-lactam and metronidazole (presumably to cover anaerobic bacteria). Each of these would constitute a therapeutic course and not surgical prophylaxis, as intended by the NDOH STG (NDOH, 2012).

Criteria (Guidelines)		Threshold	Score
■ <b>Indication</b>	➤ Surgical prophylaxis	90%	100%
	➤ <i>Staphylococci</i> and most <i>Streptococci</i> infections		
■ <b>Dose</b>	➤ Surgical prophylaxis: 1g at induction, repeated 4hourly during prolonged surgery	95%	100%
	➤ <i>Staphylococci</i> and most <i>Streptococci</i> infections: IM or IV, 0.5-1g 6-12 hourly; max 6g/day		
	➤ renal impairment : dose adjustment as follows:		
	<ul style="list-style-type: none"> <li>• eGFR 10-50ml/min, 100% of dose 12 hourly</li> <li>• eGFR&lt; 10ml/min, 50% of dose 24-48 hourly</li> </ul>		
■ <b>Duration</b>	➤ Surgical prophylaxis: single dose	95%	0%
	➤ <i>Staphylococci</i> and most <i>Streptococci</i> infections: 5-7 days		
■ <b>Contraindications</b>	➤ Previous severe immediate-type hypersensitivity to any penicillin or cephalosporin	100%	100%
■ <b>Drug interactions - To be used with caution:</b>	➤ Warfarin, NSAIDs, oral contraception, probenecid	90%	100%
■ <b>Outcome</b>	➤ No initiation of a therapeutic course of antibiotics post-delivery	90%	0%
	➤ Negative cultures		
	➤ No septicemia		

**Table 4.6: MUE criteria for cefazolin use as applied to actual practice**

#### 4.2.5 Compliance to guidelines

A predetermined set of criteria with threshold values was set to measure the level of compliance to the STG. According to the results presented in Table 4.6 above, there was 100% compliance with regard to the indication and dose for which cefazolin was used. However, every case the correct duration was not prescribed. Patients were administered more than one dose of cefazolin, hence a compliance score of 0% for that particular criterion was recorded. Another particular criterion in which a 0% score was recorded was the prescription of therapeutic antibiotics post-delivery. Overall, the review indicated that there was non-compliance to the guidelines presented in the STG.



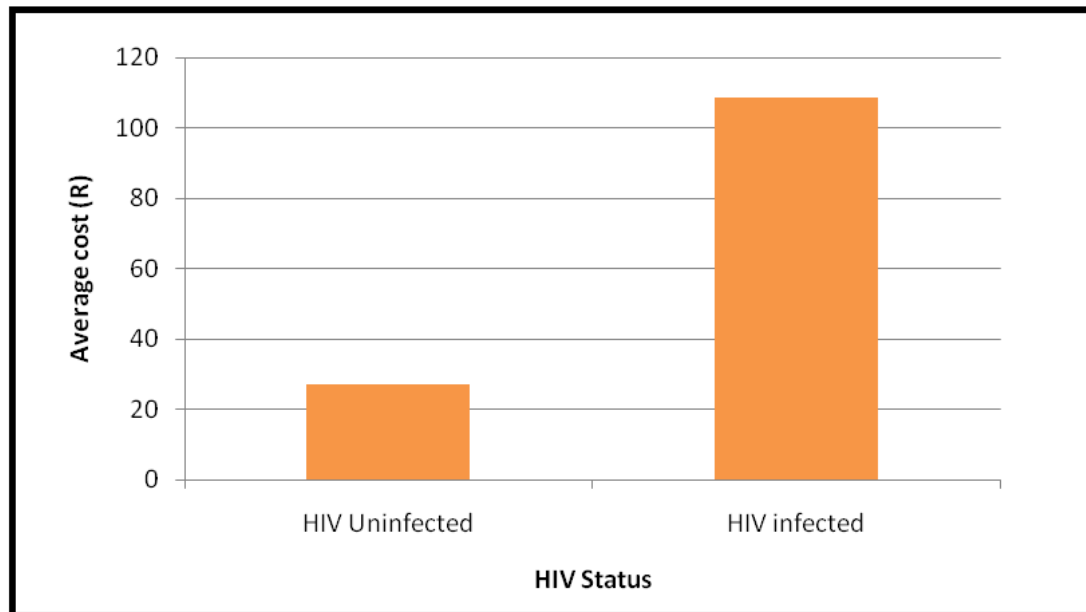
#### **4.2.6 Cost analysis**

The total and average medicine cost was calculated as per the cost per unit for each antimicrobial given intravenously and orally, using the prevailing tender price as charged to the facility by the Gauteng provincial depot. Only the direct medicine cost was taken into consideration, and not the cost of administration. The current unit cost prices at the time of the study were:

- Cefazolin 1g vial: R4.43
- Metronidazole 500mg vial: R6.13 `
- Amoxicillin 500mg capsules 15s: R7.87
- Metronidazole 400mg tablets 21s: R4.76

The total and average medicine cost was calculated for the study period (April, May and June 2016) for all patients who received antibiotics in the ward post-operatively and after discharge. This was inclusive of all intravenous antibiotics received (whether 1 or 3 day courses) and post-discharge oral antibiotics. As no stock shortages were experienced during the study period, all patients received the same medicines, as prescribed. It was found that the total cost of intravenous antibiotics for HIV-uninfected patients amounted to R1103.07, with a mean of R13.29 per patient. The total cost for HIV-infected patients was R3516.48, with a mean of R95.04 per patient. The cost for each HIV-infected patient was therefore more than seven times the cost for an HIV-uninfected patient. The total cost for post-discharge antibiotics amounted to R1515.60 with an average of R12.63 per patient. When combined, the total costs for all HIV-infected were R3983.79 (mean R107.67 per patient) and for HIV-uninfected R2151.36 (mean R25.92 per patient), as shown in Figure 4.5. A total of R5603.55 would have been saved had every patient received the stat dose as stipulated in the national guidelines, R103.24 saved per HIV-infected patient and R21.49 saved per HIV-uninfected patient.

**Figure 4.5: Average Cost for Medication supplied per patient**



### 4.3 Qualitative data

Only 7 medical officers were available to participate in the interviews. The majority of non-respondents indicated that they were busy or did not perform CS often enough to provide meaningful comment. Heidelberg Hospital has a small maternity ward, hence only a limited number of medical officers perform CS on a regular basis. Informed consent was obtained from all medical officers prior to participation and confidentiality was assured. Responses were recorded verbatim. The data were themed according to their responses and entered into Microsoft Excel, to generate a frequency table (shown in Table 4.7) and analysed.

VARIABLE	FREQUENCY N (%)
<i>Negative experiences regarding post-Caesarean section infections</i>	
Common	0 (0)
Rare	7 (100)
<i>Personal experiences have affected prescribing practices in relation to antibiotic prophylaxis in CS</i>	
Yes	3 (42.9)
No	4 (57.1)
<i>There is a protocol in place for the administration of antibiotic prophylaxis in patients undergoing CS</i>	
Yes	5 (71.4)
No	1 (14.3)
Unsure	1 (14.3)
<i>Prescriber is personally familiar with the antibiotic prophylaxis recommendations included in the National Department of Health Standard Treatment Guidelines</i>	
Yes	4 (57.1)
No	3 (42.9)

*Details of the pre- and post-operative antibiotic prophylaxis regimen used in CS*

**Pre-op:** Cefazolin 1g IVI

**Post-op:** Cefazolin 7 (100)

**Post-discharge:** Amoxicillin & Metronidazole

*Doses prescribed and duration*

**Pre-op:** 1g < 60 minutes before the first incision

**Post-op:** 1g 8 hourly IVI over 24 hour period (3 Doses)

**Post-discharge:** 7 (100)

Amoxicillin 500mg 8 hourly P.O over a 5 day period

Metronidazole 400mg 8 hourly P.O over a 5 day period

*Specific reasons for the regimen and duration exist*

Yes 4 (57.1)

No 3 (42.9)

*Doses used for HIV-positive patients*

**Pre-op:** Cefazolin 1g IVI < 60 minutes before the first incision

**Post-op:** Cefazolin 1g every 8 hours IVI for 3 days (9 doses)

Metronidazole 500mg every 8 hours IVI for 3 days (9 doses) 7 (100)

**Post-discharge:** Amoxicillin 500mg every 8 hours P.O for 5 days

Metronidazole 400mg every 8 hours P.O for 5 days

*Feelings about having to follow a different prophylactic regimen from that stated in the NDOH STG*

Willing to follow new recommendation provided there is evidence-based research 6 (85.7)

Not willing since there is no problems with the current regimen 1 (14.3)

*Need for changes in the NDOH STG regarding CS antibiotic prophylaxis*

Yes	7 (100)
No	0 (0)

**Table 4.7: Frequency table depicting themed codes for responses**

All medical officers reported that, in their own experience, post-CS infections at Heidelberg Hospital were rare. Respondent 4 made a subtle change to that response, though, claiming that post-CS infections were:

*“not common however infections seem to be higher in summer, ecological factors play a role and common in obese people.”*

According to respondent 6, rates of infection were:

*“very low, post CS infections are often related to the indication of CS, the nature of labour and immunological state”*

Despite acknowledging that their personal experiences of post-CS sepsis were rare, 3/7 respondents (42.9%) felt that their personal experiences in the past had affected their prescribing practices in relation to antibiotic prophylaxis in CS. Respondent 1 felt that factors to be borne in mind included:

*“a rarely fumigated theatre and a lot of immunocompromised patients”*

Respondent 3 said that it was important to:

*“judge the situation as other bacteria is present, Kefzol covers a broader spectrum.”*

Respondent 4 felt that the:

*“outcome is different depending on cases eg, malnutrition, prolonged labour, immunocompromised patients especially in HIV-positive patients.”*

On the other hand, respondent 2 felt that prescribing practices would differ in the case of established sepsis:

*“if there is an infection in the ward then stay will be extended to 5 days.”*

Respondent 6 indicated that prescribing choices were not affected by specific patient factors, such as patient body mass:

*“prophylaxis is standard even for obese patients.”*

The majority of the respondents (5/7, 71.4%) was aware that there was a hospital-specific protocol in place for the administration of antibiotic prophylaxis in patients undergoing CS. Interestingly, though, respondent 2 indicated that there was no particular protocol in place as:

*“this is the hospital practice and they follow recommendations from the morbidity and mortality meetings.”*

Almost half (3/7, 42.9%) could provide no specific reasons for following the existing protocol, beyond that it was hospital policy. Others did provide reasons, including:

*“Kefzol is a 1<sup>st</sup> grade (sic)cephalosporin and it is good if it is an invasive surgical procedure, to reduce chances of resistance and in case of poor response there is a lot of other antibiotics available.”* (Respondent 1)

*“Has an extended spectrum and HIV-positive patients are more susceptible to infections.”* (Respondent 2)

*“Kefzol has a broad spectrum cover for most surgical procedure.”* (Respondent 3)

*“A smaller theatre is being currently used, dangerous practices as is not as hygienic, this regimen is standard and common in most hospitals so its hospital policy. Patient treatment is individualised.”*(Respondent 4)

Just over half of the respondents (4/7, 57.1%) were familiar with the antibiotic prophylaxis recommendations included in the National Department of Health Standard Treatment Guidelines.

Despite knowing about the NDOH STG, there was unanimous agreement that HIV-positive patients should receive intravenous antibiotics for 3 days (9 doses), by virtue of their being immunocompromised. Respondent 2 added that the:

*“CD4 count is not always available so Flagyl is added to extend the spectrum of antibiotic activity since patients are immunocompromised.”*

In terms of their feelings about having to follow a different prophylactic regimen from that stated in the NDOH STGs, almost all respondents (6/7, 85.7%) were willing to follow new recommendations, provided they were evidence-based. Respondent 4 suggested that:

*“resistance and ecological changes should be taken into account and more money should be invested in investigating alternative regimens.”*

Only one respondent (respondent 5) was not willing to change practice, as he felt that there were no problems with the current recommendations in the STG and stated:

*“if it is working there is no need to change it unless the rate of sepsis increases.”*

All 7 medical officers had suggestions for changes or recommendations for consideration in the Standard Treatment Guidelines regarding antibiotic prophylaxis in CS, as follows:

*“Conduct studies to see trends of infections in immunocompromised patients and those with stronger immunity and conduct studies to find common pathogens that are the culprit for sepsis in the area before changes are made.”* (Respondent 1)

*“HIV positive patients should be considered, extend 1g Kefzol to 3 more doses in the STG.”* (Respondent 2)

*“STG needs to provide more information, STG should be specific for district and tertiary levels, consider other antibiotics by identifying common bacteria that causes sepsis, Kefzol is cheap and effective and comfortable with it.”* (Respondent 3)

*“To avoid confusion let doctors know that the MCG is available, STG needs more improvement and more information with regard to maternal care, a part of Millennium Development Goals was to improve maternal care therefore the MCG<sup>i</sup> and STG should be consolidated.”* (Respondent 4)

*“There is no need for post op antibiotics if there are no complications with the exception of HIV positive patients.”* (Respondent 5)

*“STG does not take into account the patient and should be more patient-centred, there are different schools of medicine therefore there is a need for more consolidated and unified information.”* (Respondent 6)

*“Add more broad spectrum antibiotics, consider Augmentin (a penicillin) for prophylaxis.”* (Respondent 7)

#### **4.4 Summary**

Both quantitative and qualitative data showed that antibiotic prophylaxis practice after CS at Heidelberg Hospital did not follow the NDOH STG, but consistently followed a local hospital policy, supposedly based on local experiences, and specifically aimed at providing a greater degree of protection to patients identified as HIV-positive and hence assumed to be immunocompromised. In addition to extended courses of IV antibiotics (either 3 or 9 doses,

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<sup>i</sup>MCG refers to the Maternal Care Guidelines

including IV metronidazole in the latter cases, as opposed to the single dose cefazolin prescribed in the STG), all patients who underwent a CS delivery were discharged with an additional 5 days' of oral antibiotics.

The implications of these finding are considered in Chapter V.



## CHAPTER V: DISCUSSION

### 5.1 Introduction

The purpose of this chapter is to elaborate on the results provided in Chapter 4 and to place these in the context of the available literature. This chapter highlights the interpretation of the quantitative and qualitative results. It looks at the extent of non-compliance with national guidelines and provides possible reasons for such non-compliance.

### 5.2 Medicine Use Evaluation

#### *5.2.1 Reasons for CS and choice of prophylactic regimen*

Studies have indicated that, as parity increases, so does the incidence of haemostatic problems (Moodliar *et al.*, 2007). HIV status was applied, regardless of gravidity or age, to decide whether women received 3 or 9 doses of intravenous antibiotics. In addition, those on the 3-day course also received IV metronidazole, and all patients were discharged with an additional 5 days' of oral antibiotics. This was in direct contradiction of the existing NDOH guidance, which called for a single dose of IV cefazolin, within an hour of the first incision.

In the current study the complications which prompted a CS were seen among all age groups. However, as expected, the incidence of infectious complications post-CS was very limited, so a connection cannot be made between age, parity or HIV status and complications.

The recorded indication for a CS also did not correlate with the duration of prophylactic antibiotics. The most prevalent indication for a CS was a previous CS, accounting for 28.3% of cases. This finding is consistent with the literature. The next most prevalent indication, regardless of HIV status, was CPD (22.5%) and foetal distress (22.5%). In a study conducted by Gidiri and Ziruma (2014) in Zimbabwe, the most prevalent indication for CS was also a previous CS, followed by foetal distress and CPD.

Similar findings were reported by Naidoo and Moodley (2009), who contrasted the foetal distress rates in South Africa and the UK. Conservative measures should be considered before a

decision is made to perform a CS and failure to progress maybe one indication to consider. The authors also suggested that CPD should be excluded by conducting skilled pelvic examination and that careful utilisation of oxytocin to augment labour may help to avoid unnecessary CS without affecting foetal outcomes. Nonetheless, inexperienced medical officers may be hesitant to resort to such measures as they fear litigation and will have to provide intense foetal and maternal monitoring to prevent uterine hyperstimulation and subsequent foetal distress.

According to the available literature, patients living with HIV have a higher risk of complications. However, in the current study, patients reported to be HIV-negative were shown to have a higher rate of complications requiring CS. The number of such cases was, however limited, and the result may be an effect of chance. Patients' HIV status did not appear to play a direct role in terms of complications, but was directly and invariably responsible for the duration of antibiotic use. Evidence from the literature, and in particular from the systematic review conducted by Calvert and Ronsmans (2013), suggest that the risk of intrauterine infections during pregnancy, delivery or the post-partum is increased due to HIV. Women living with HIV who delivered vaginally or through CS were shown to have over three times the risk of puerperal sepsis when compared with uninfected women. However, the degree of immunosuppression is important. Ferrero and Bentivoglio (2003) showed that the incidence of complications was significantly increased in HIV-positive mothers when their CD4 lymphocytes count fell below  $500 \times 10^6/l$ . Unfortunately, in the current study the patients' viral load and CD4 cell count was not available at the time of admission. A rapid HIV test was done to check HIV status, but the degree of immunosuppression was not considered. As much of the pregnancy-related mortality seen in women living with HIV is not likely to be a result of direct obstetric complications, it is crucially important that high quality antenatal and delivery services are provided to all pregnant women, and that timeous initiation of antiretroviral therapy (ART) is achieved in those living with HIV. Thus, while there is a theoretical benefit from the provision of prophylactic antibiotics to women living with HIV undergoing CS, in order to reduce their risk of intrauterine infections, the blanket provision of 3 days' prophylaxis is questionable. The 8 days' course provided can only be characterised as an unnecessary therapeutic course, and not as prophylaxis.

### 5.2.2 Reasons for extended antibiotic regimens

Over 3 decades, researchers have reported that almost 50% of antibiotics used in hospitals are used inappropriately (Goldmann *et al.*, 1996). Despite this, not much has been achieved to reduce costs and the selection pressure for drug-resistant bacteria. The misuse of antibiotics in CS has become a particular problem at Heidelberg Hospital. As seen in this study, 85% of patients did not have a particular reason to receive extended post-operative antibiotics in an attempt to prevent SSIs. The treatment was nevertheless entirely compliant with a local practice standard, and consistently based on the patients' HIV status.

Dhar *et al.* (2014) have shown that prolonged labour with frequent vaginal examinations and PROM may contribute to increased infection rates in such cases. In addition, the length of time between the rupture of the membranes and surgical intervention contributes to the infection rate post-CS (Gould, 2007). The small number of patients (5.8%) in this study who might have been considered to deserve a full therapeutic course of antibiotics, because of an identified complication, still received a course determined by their HIV status. In 85.7% of these supposedly complicated cases, the patient was HIV-uninfected, and therefore received only 3 doses of IV cefazolin. If the reason for their complicated status is accepted as justifying a full therapeutic course, as guided by the draft Maternity Care Guidelines (Department of Health, 2016) they might be considered to be under-treated. However, even when only a single day of IV antibiotics was prescribed, all patients, regardless of HIV status or diagnosed complications, were discharged with an additional 5 days' of oral antibiotics.

The findings of this study were important, given the increasing rates of CS in South Africa. Mugford *et al.* (1989) have highlighted that reducing the number of avoidable CS will help reduce the infection rate post-CS. In the current study, only 1.7% of CS were performed electively, without any documentation of a complication requiring a CS. Mugford *et al.* (1989) also emphasised the need to practise and maintain good sterile surgical techniques, in a suitably sterile operating theatre. In this regard it is worth noting that the Heidelberg Hospital theatre is a temporary structure, currently being used after the previous theatre was damaged in a fire. The air quality and sterility of the theatre may therefore not meet all requirements.

The development of SSIs can be a very daunting experience for a clinician. Wound infections in patients who had surgeries are still observed to be the most common nosocomial infections (Smyth and Emmerson, 2000). In the current study only one case of post-CS sepsis was reported in the 3 month study period.

Apart from post-CS SSIs contributing to maternal morbidity, they also prolong the duration of hospital stay, further increasing costs. In a study by Dhar *et al.* (2014), women who had CS deliveries were normally discharged on the third post-operative day. However, this stay was extended to an average of 5-8 days should a woman develop an SSI in the hospital. At Heidelberg Hospital, HIV-positive patients were generally discharged after the third day and only kept longer in the event of an infection (Dhar *et al.*, 2014). However, the initial extension in the length of stay could be directly related to the prescription of 3 days' of IV antibiotics.

### ***5.2.3 Compliance with national standard treatment guidelines***

The results from the MUE confirmed the level of non-compliance with the NDOH STG. The indication for which cefazolin was being used was appropriate, as it was administered for surgical prophylaxis. The dose of 1g initially prescribed was in accordance with the STG. However there was 0% compliance in respect of the duration of treatment. Since the duration of the procedure was always less than 60 minutes, a single dose would have sufficed. However, in all cases, multiple doses were given post-operatively. There was also 0% compliance in the outcome, as therapeutic courses of antibiotics had been initiated.

### ***5.2.4 Cost analysis***

There was a considerable difference in the costs for HIV-negative and HIV-positive patients. The cost of IV antibiotics for HIV-positive patients was more than seven times higher than that for HIV-negative patients. The impact on the pharmacy budget would therefore have been considerable, with little or no justification. A similar practice was also documented in a study by Gidiri and Ziruma (2014), in which patients were given intravenous treatment in addition to a standardised course of antibiotics for a week; and received amoxicillin 500mg three times a day for 7 days, metronidazole 400mg three times a day for 7 days from the first post-operative day. This practice was thus similar to what was shown at Heidelberg Hospital. Gidiri and Ziruma (2014) found no statistically significant difference in patients who received a single (*stat*) dose of antibiotic prophylaxis compared to those who received treatment for a week. The available literature also provides convincing evidence that a single dose of antibiotics is effective in preventing post-surgical wound infections (Hedrick and Sawyer, 2012). The existing NDOH policy of routine prophylaxis with a single dose of an IV antibiotic such as cefazolin would be

expected to be effective in preventing SSIs post-operatively, and therefore be cost effective. The chances of poor adherence to the post-discharge oral antibiotics might be high, also contributing to fruitless expenditure. In addition, the chances of adverse effects to antibiotics are raised with extended courses, potentially adding further avoidable costs (Mugford *et al.*, 1989).

Despite local medical practitioners having knowledge of the existing NDOH guidelines, they have developed local standards of practice which entrench prolonged use of antibiotics. This inevitably places added pressure on nurses by increasing the workload in an already understaffed hospital, increasing the costs to patients as well as the healthcare system.

### 5.3 Qualitative data

The quantitative results from the MUE showed a high level of non-compliance with the NDOH STGs. The qualitative portion of the study sought to uncover possible reasons for this non-compliance, based on the perceptions and fears of the local medical practitioners and their expressed logical basis for their prescribing patterns. Heidelberg Hospital is a district hospital with a limited number of medical officers who perform CS. Hence not all the medical officers are familiar with current practices regarding antibiotic prophylaxis, which is explained by the small number of respondents. A lack of time to engage with the study also hampered achievement of a higher response rate.

According to the interview data, local medical officers regarded post-CS infections as very rare at Heidelberg Hospital. During the 3 month study period, which was all in the winter months, only 1 patient was readmitted for sepsis after a CS. Despite this rarity, the clinicians were of the opinion that there were discernible risk factors. For example, Respondent 4 claimed that *“infections seem to be higher in summer”* and that *“ecological factors play a role”*.

Although 57.1% of the respondents stated that their own personal experiences had not affected their prescribing practices, the majority were comfortable to follow the standard hospital policy, contrary to the NDOH STG. In terms of the local standard, prolonged therapeutic courses were not based on identified or suspected sepsis, but purely on the basis of HIV status. Respondent 6 noted the lack of individualised care, for example that *“prophylaxis is standard even for obese patients”*. It is notable that the literature supports the concern that obese patients are at higher risk of developing infections (Wloch *et al.*, 2012). The current NDOH STG does not allow for

adjustment of prophylactic doses in obese patients, even though this may be warranted on the basis of pharmacokinetic considerations.

Although only 71.4% of respondents stated that they were aware of the hospital protocol regarding prophylaxis, the majority claimed to be following *“hospital policy”*. Only 57.1% were familiar with the recommendations stated in the NDOH STGs. Interestingly, Respondent 2 indicated that there was no particular protocol in place, but that *“this is the hospital practice and they follow recommendations from the morbidity and mortality meetings.”* After the researcher asked to see the protocol, no written document could be produced. Nonetheless, the MUE demonstrated the consistent application of a local policy on antibiotic prophylaxis in CS. In such a setting, newly appointed and inexperienced medical officers will tend to follow the practices of more senior staff, or their peers, regardless of the existence of the NDOH STGs. A majority of the respondents (57.1%) claimed to have specific reasons for following the local regimen. The remainder (42.9%) seemed to be comfortable merely following what they were told was hospital policy. Among the reasons cited was that *“Kefzol is a 1<sup>st</sup> grade (sic) cephalosporin and it is good if it is an invasive surgical procedure, to reduce chances of resistance and in case of poor response there is a lot of other antibiotics available.”* Although the choice of a first-generation cephalosporin is appropriate, this does not explain the extended duration, the addition of metronidazole in the 3-day regimen, or the decision to add a full 5-day course of post-discharge oral antibiotics. It was claimed that *“this regimen is standard and common in most hospitals so its hospital policy”*. The claim that *“patient treatment is individualised”* in the event of an infection would appear to describe standard practice, but could not be confirmed with any certainty from the sample drawn. While it is true that there are *“a lot of other antibiotics available”*, that does not excuse putting the first-line prophylactic choice at risk by overuse, potentially increasing the risk of selecting resistant hospital organisms.

An element that could not be as easily dismissed was the concern about the standard of the facilities being used. Respondent 4 indicated that *“[a] smaller theatre is being currently used”*, and that *“dangerous practices”* were being followed, and that the facility *“is not as hygienic”*. Unfortunately, Heidelberg Hospital’s operating theatre does not currently allow for the practice of appropriate aseptic techniques as the theatre is still under reconstruction. The WHO requires the maintenance of a proper ventilation system in operating theatres, with around 20 air changes per hour required to maintain constant air quality (WHO, 2016b).

With regard to the pre-and post-operative antibiotic regimen used, although this did not strictly constitute “prophylaxis”, all the respondents held that this was an appropriate regimen. A similar regimen was reported by Gidiri and Ziruma (2014) in Zimbabwe, where it was standard practice to administer an extended course of antibiotics, even in the absence of an established or suspected infection.

All of the respondents stated their support for the extended regimen used in women living with HIV, and justified this by reference to the “*immunocompromised*” state of the patients. Respondent 2 added that the “*CD4 count is not always available so Flagyl is added to extend the spectrum of antibiotic activity since patients are immunocompromised.*” While it is true that studies have reported that HIV-infected women who give birth by CS have a considerably increased incidence of complications (Semprini *et al.*, 1995), this heightened risk is correlated with the extent of immune compromise (Moodliar *et al.*, 2007). Although the numbers were small, the current study did not appear to confirm an increased risk of post-CS infection in women living with HIV. However, none of the clinical notes provided evidence of either viral load or CD4 measurements. The blanket administration of 9 doses of combined IV antibiotics, followed by 5 more days’ of oral antibiotics can therefore not be justified. Since the NDOH has now mandated a test-and-treat approach to patients living with HIV, including pregnant women, there should be no delay in initiating ART. Although CD4 counts have been relied upon in the past, a better measure of the degree of control achieved through ART would be a viral load, taken before CS. However, the practicality of such a policy in a district hospital might still be questioned. In the event of an unknown viral load, the question still remains whether an extended duration of prophylaxis is needed, in the absence of complications that might indicate the need for a full therapeutic course.

The 2015 draft “Guidelines for Maternity Care in South Africa - A manual for clinics, community health centres and district hospitals” (Department of Health, 2015) state that “Caesarean section is associated with an increased risk of maternal infection, haemorrhage, thromboembolism, postpartum death, and obstetric complications in subsequent pregnancies. Women who ask for Caesarean section and have no clinical indication for the operation should be counselled about the risks and benefits of the procedure.” They mandated that “[j]ust before starting the operation, ensure that: .....[a] broad-spectrum prophylactic intravenous antibiotic is given, e.g. cefazolin 1 g, irrespective of whether the operation is an emergency or elective procedure.” (pg 55) However, three later mentions give conflicting advice, as follows: (pg 56): “Prescribe additional (therapeutic) doses of antibiotics for 24 hours to 5 days in women who

have risk factors for infection, (e.g. all HIV infected women; prolonged labour or prolonged ruptured membranes; Caesarean section in second stage labour, chorioamnionitis, >5 vaginal examinations during labour, when the fetal head needed to be pushed up vaginally); pg (139): “Prophylactic antibiotics are given for both elective and emergency Caesarean section: Cefazolin 1 g IVI when on the operating table prior to the start of surgery, followed by a broad-spectrum antibiotic for 3-5 days”; and (pg164): “Women with risk factors for infection (HIV infection, prolonged labour, prolonged rupture of membranes, chorioamnionitis, or Caesarean section in the second stage) may need to be kept in hospital on antibiotics for 3-5 days.” However, the 2016 (current) draft (Department of Health, 2016) has altered this advice somewhat: (pg 47): “Just before starting the operation, ensure that: .....Broad-spectrum intravenous antibiotics have been given. These may be either prophylactic or therapeutic antibiotics. Routinely, a dose of prophylactic antibiotics (e.g. cefazolin 1g) is given pre-op, irrespective of whether the operation is an emergency or elective procedure, and there is no need to give further doses of antibiotics post-op. If, however, the patient has evidence of intra-uterine sepsis, or there are factors which put her at high risk of post-operative sepsis, then intravenous therapeutic antibiotics (e.g co-amoxycylav 1.2g) should be started pre-op and continued post-op for five days, although intravenous antibiotics could be changed to oral antibiotics after a few days depending on the patient’s condition.” The guidelines further state that: “Indications for therapeutic rather than prophylactic antibiotics include:

- severe immunocompromise (e.g. history of recent AIDS defining illness or CD4 <250)
- evidence of chorioamnionitis (including offensive liquor)
- prolonged labour with many per vaginal examinations after rupture of membranes
- obstructed labour (will usually have systemic signs of sepsis)
- Caesarean delivery following failed vacuum extraction.”

A subtle change in thinking is evident in this progression in the guidelines from the 2015 to the 2016 drafts, but the guidance is still at variance with the NDOH STGs, and that conflict has yet to be resolved. The concern with avoiding all post-operative maternal sepsis by any means is at loggerheads with the need to conserve antimicrobials through restricting unnecessary use.

It was striking that 85.7% of the respondents were willing to follow new recommendations provided they relied on evidence-based research. Only one respondent (14.3%) was satisfied with the current recommendation provided in the STG, and felt that it did not need to be changed: *“if it is working there is no need to change it unless the rate of sepsis increases.”* The onus would, however, seem to be on those who wish to change the existing STG, which is based



on global evidence, rather than on the National Essential Medicines List Committee (NEMLC) to justify their guideline. The drafters of the Guidelines for Maternity Care in South Africa also need to provide clear evidence to justify full therapeutic courses of antibiotics in each of the circumstances listed in the 2016 draft document, if these are to supersede the STGs (and force a change in the latter document).

Notably, every respondent had suggestions for consideration by the NEMLC, and were of the opinion that the current STG had insufficient information with regard to maternal health and antibiotic prophylaxis for CS (as opposed to all pelvic surgery) and that there was a need for a more *“consolidated and unified guide”*. Suggestions for making the guidance *“more patient-centred”* and considering HIV-positive patients were put forward. This would appear to be a reasonable request as the current STG does not take into account such factors as body mass or immune dysfunction.

Respondent 1 suggested that studies be conducted *“to see trends of infections in immunocompromised patients and those with stronger immunity and conduct studies to find common pathogens that are the culprit for sepsis in the area before changes are made.”* Respondent 2 indicated that *“HIV positive patients should be considered”* and suggested that the guidelines *“extend 1g Kefzol to 3 more doses in the STG”*. Respondent 3 also suggested that there was a need to *“consider other antibiotics by identifying common bacteria that causes sepsis”*. Respondent 5 was content with the current guidance for a stat dose, but indicated that *“[t]here is no need for post op antibiotics if there are no complications with the exception of HIV-positive patients”*. Respondent 7 indicated that *“more broad spectrum antibiotics”* should be added, and suggested *“Augmentin (a penicillin) for prophylaxis”*. As discussed in chapter II, the choice of a first-generation cephalosporin such as cefazolin has broad support. Whether additional epidemiological studies are necessary to track local causative organisms and their sensitivity patterns is therefore open to question. However, given the prominence of HIV as a contributing factor to excessive maternal morbidity and mortality, some consideration of the potential impact of HIV infection on the choice of prophylactic antibiotic regimens in CS seems warranted.

#### **5.4 Appropriate remedial actions identified**

The results of this study provide clear evidence of non-compliance with existing STGs. Although local Drug and Therapeutics Committees are empowered to consider the need for local policies, in the absence of clear evidence for a change, the issue of prophylactic regimens in CS needs to be decided at higher levels, at provincial and national level. There would seem to be sufficient evidence for reconsideration of the local hospital protocol, as it does not appear to be evidence-based and is evidently contributing to increased workload and costs.

#### **5.5 The need to review the NDOH STG**

Insufficient evidence has been provided by the current study to motivate for changes to be made to the regimen for antibiotic prophylaxis in CS stipulated in the current NDOH STG. The administration of a single dose of cefazolin IV before commencing a CS is consistent with and supported by the recently launched WHO guidelines on preventing surgical site infections, published on 3 November 2016. The WHO strongly recommends that surgical antibiotic prophylaxis be administered within 120 minutes prior to the first incision also taking in to account the half-life of the antibiotic. In order for the antibiotic to provide a protective effect, the antibiotic should be present in the affected tissues at an adequate concentration at the time of incision and during the procedure. For this reason antibiotics should be administered before the incision. WHO also recommended that administration of antibiotics with a short half-life (such as cefazolin, cefoxitin and penicillins in general) should be done closer to the time of incision (less than 60minutes as stated in the current STG) so that the protective effect will persist. Several other guidelines, such as those published by the ASHP (Bratzler *et al.*, 2013) and SHEA/ IDSA (Anderson *et al.*, 2014), support the administration of prophylaxis within 60 minutes prior to incision and recommend its discontinuation within 24 hours post-operatively. It is very important to note that WHO strongly recommended against the prolongation of surgical antibiotic prophylaxis (SAP) being administered post-operatively for the purpose of preventing SSI. Based on the available evidence, and also taking into account the possible adverse events and potential risk of the emergence of antimicrobial resistance associated with the prolonged use of SAP, a meta-analysis of 44 randomised clinical trials (RCTs) confirmed that prolonged SAP post-operatively had no benefit in the reduction of surgical-related wound infections as opposed to a single dose (WHO, 2016b). Hence there is no need for modifications of the

antibiotic prophylaxis regimen stated in the STG, and certainly no need to prolong prophylaxis post-operatively and post-discharge.

Maternal mortality has thus drawn the attention of many and has been regarded as one of the most sensitive topics. Much emphasis has been placed on achieving equitable progress to help lower the disproportionate burden of poor maternal health in low- and middle-income countries, but much is yet to be done. Since the MDG5 target of a 75% reduction in maternal mortality was not met, there is a need for health systems to act in response to the changing context of women's lives, as urbanisation has not contributed to quality of care for everyone and there is a great need to make information more accessible. The risk of a woman dying as a result of pregnancy and child birth is more than 100 times greater in sub-Saharan Africa compared to in high-income countries (Koblinsky *et al.*, 2016). In high-income countries, there have been successful medical interventions that have contributed to much lower maternal and neonatal mortality. However doubts have been expressed as to whether the care given was evidence-based, and as a result, medical liability costs can be very high (Shaw *et al.*, 2016). The challenges faced by health systems regarding poor quality and inaccessible care are constant, despite the improved economic or political stability of developing countries. Communities will need to put increased pressure on national and regional governments for better harness domestic health spending to provide universal health coverage, hence effectively addressing maternal health and achieving sustainable improvements in the quality of care (Koblinsky *et al.*, 2016).

## **5.6 Limitations**

There were several limitations to the present study. The sample size for the qualitative phase was small. There was also absence of data in some medical records, such as the exact timing of each antibiotic administration, patients BMI values as well as the viral load and CD4 cell count of HIV infected patients. There were several cases with incomplete data hence it was not possible to confirm all cases were recorded due to insufficient doctors' notes.

## **5.7 Summary**

This chapter provided an analysis and discussion of the results. It provided an analysis of the implications of the identified non-compliance with the NDOH STG, the reasons for such non-compliance as well as the appropriate remedial actions to be taken on the basis of the results obtained in the study. It also included the limitations of the study.

## **CHAPTER VI: CONCLUSIONS AND RECOMMENDATIONS**

### **6.1 Introduction**

The final chapter highlights the overall conclusions of the study, in addition to providing recommendations for further research.

### **6.2 Conclusions**

Maternal health has demanded the attention of many and has been made a global priority. As a result, much focus should be placed on ensuring that pregnant women have access to quality care, including quality CS deliveries were warranted. That includes taking all necessary steps to avoid the occurrence of post-operative SSI. Part of that effort must include the provision of appropriate antibiotic prophylaxis, administered at the right time, in the right dose, by the right route of administration and for the right duration. The injudicious use of antibiotics has contributed to the emergence of antimicrobial resistance. One form of injudicious use is the prolonged administration of prophylactic antibiotics in the absence of an established or suspected infection.

This study provides clear evidence that the provision of antibiotic prophylaxis for women undergoing CS delivery at Heidelberg Hospital, a district hospital situated in Gauteng was irrational. Using MUE methods, the study identified different elements of non-compliance with the NDOH standard treatment guidelines. Although the right prophylactic antibiotic (cefazolin) was initially prescribed, in all cases, a prolonged course was administered. In those women not living with HIV, administration was extended for 3 doses instead of one. However, in those women living with HIV, intravenous administration was extended for 3 days, accompanied with intravenous metronidazole. All women who had delivered by CS, whether living with HIV or not, were also provided with an additional 5 days of oral antibiotics. There was insufficient evidence to support the use of therapeutic courses of antibiotics in the women treated at Heidelberg Hospital.

Not only would this non-compliance with the STG have contributed to the selective pressure that potentially results in increased resistance, it would also have increased the costs incurred

and contributed to additional nurse workload on the wards. Although the use of extended duration antibiotic resistance was justified by the prescribers on the basis of assumed increased risk in those who were presumably immunocompromised, as well as the conditions at the hospital which prevented the use of appropriate aseptic techniques, the treatment regimen developed and implemented locally is not supported by the existing evidence from the literature. Nonetheless, there is mitigating evidence in the form of the draft Maternal Care guidelines, which have supported the use of extended dosing in women at presumed higher risk of SSI. The study did not provide any justifications for the therapeutic use of antibiotics in patients without established or suspected infections post-CS. Instead, the literature summarised for this study has provided evidence for the reconsideration of the local hospital protocol. However, there is also a need to reconcile the advice provided in the STG with that provided in the Maternal Care guidelines. Although the concern for maternal welfare is genuine, and the avoidance of preventable complications has been highlighted by the Confidential Enquiries into Maternal Mortality, there is still a need to enforce antibiotic stewardship in order to limit the development of resistance. Clear support for an unambiguous prophylactic antibiotic regimen in CS should be signalled, both in the NDOH STG and in any other NDOH policies, such as the Maternal Care guidelines.

### **6.3 Recommendations for remedial action**

The following recommendations are offered:

- the NDOH STG should be made explicit, replacing the “pelvic surgery” entry with an unambiguous recommendations for use in women undergoing CS;
- this STG should support the single-dose regimen of cefazolin IV;
- clear guidance should be provided, both in the STG and the Maternal Care guidelines, on the management of women suspected of having an established infection, and who deserve a full therapeutic course of antibiotics;
- this guidance should be specific about the choice of antibiotic(s), the route(s) of administration, and duration;
- routine monitoring and evaluation systems should be put in place to track compliance with the guidelines and identify areas for intervention; and
- the results of this study should be shared with the Heidelberg Hospital Drug and Therapeutics Committee, the Gauteng provincial Pharmacy and Therapeutics

Committee, and the relevant antimicrobial stewardship structures, in order to inform the development of remedial action.

#### **6.4 Recommendations for further research**

This study has also identified opportunities for further research, including:

- identifying patients readmitted for sepsis after CS delivery at Heidelberg Hospital, in order to identify risk factors that would justify more aggressive initial treatment;
- investigation of the reasons for resorting to CS at Heidelberg Hospital, in order to avoid unnecessary CS and the risks associated with this form of delivery.

#### **6.5 Summary**

The last chapter listed the conclusions drawn from the study, and provided recommendations for remedial action as well as for future research.

## BIBLIOGRAPHY

Abebe FE, Gebeyehu AW, Kidane AN, Eyassu GA (2016). Factors leading to cesarean section delivery at Flegehiwot referral hospital, Northwest Ethiopia: a retrospective record review. *Reprod Health* 13(6):1-7.

Academy of Managed Care Pharmacy (AMCP) (2009). Concept in Managed Care Pharmacy Series: *Pharmaceutical Care*. Available at [www.amcp.org/WorkArea/DownloadAsset.aspx?id=9296](http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=9296). (Accessed on 11 September 2016).

Akpan MR, Ahmad R, Shebl NA, Ashiru-Oredope D (2016). A review of quality measures for assessing the impact of antimicrobial stewardship programs in hospitals. *Antibiotics* 5(1):5.

Aldeyab M, Harbarth S, Vernaz N, Kearney M, Scott M, DarwishElhajji F, Aldiab M, McElnay J (2012). The impact of antibiotic use on the incidence and resistance pattern of extended-spectrum beta-lactamase-producing bacteria in primary and secondary healthcare settings. *Br J Clin Pharmacol* 74(1):171–179.

Althabe F, Sosa C, Belizán JM, Gibbons L, Jacquerioz F, Bergel E (2006). Caesarean section rates and maternal and neonatal mortality in low-, medium-, and high income countries: an ecological study. *Birth* 33(4): 270-277.

American College of Obstetricians and Gynecologists (ACOG) (2003). ACOG practice bulletin number 47: Prophylactic antibiotics in labor and delivery. *Obstet Gynecol* 102(4):875–882.

American College of Obstetricians and Gynecologists (ACOG), Women's Healthcare Physicians (2010). Committee opinion no. 465: antimicrobial prophylaxis for cesarean delivery: timing of administration. *Obstet Gynecol* 116(3):791–792.

American Society of Hospital Pharmacists (ASHP) (1993). ASHP statement on pharmaceutical care. *Am J Hosp Pharm* 50:1720–1723.

Anderson DJ, Podgorny K, Berrios-Torres SI, Bratzler DW, Dellinger EP, Greene L, Nyquist A, Saiman L, Yokoe DS, Maragakis LL, Kaye KS (2014). Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 35(6):605-627.



Andrews WW, Hauth JC, Cliver SP, Savage K, Goldenberg RL (2003). Randomized clinical trial of extended spectrum antibiotic prophylaxis with coverage for *Ureaplasmaurealyticum* to reduce post-cesarean delivery endometritis. *Obstet Gynecol* 101(6):1183–1189.

Andrews WW, Shah SR, Goldenberg RL, Cliver SP, Hauth JC, Cassell GH (1995). Association of post-cesarean delivery endometritis with colonization of the chorioamnion by *Ureaplasmaurealyticum*. *Obstet Gynecol* 85(4):509–514.

Anonymous (1998). Antibiotic prophylaxis in surgery: summary of a Swedish-Norwegian consensus conference. *Scand J Infect Dis* 30(6):547–557.

Arabashahi KS, Koohpayezade J (2006). Investigation of risk factors for surgical wound infection among teaching hospital in Tehran. *Int Wound J* 3(1):59–62.

Barrett FF, McGehee RF, Finland M (1968). Methicillin-resistant *Staphylococcus aureus* at Boston City Hospital. *N Engl J Med* 279(9):441–448.

Barros FC, Vaughan JP, Victora CG, Huttly SRA (1991). Epidemic of Caesarean sections in Brazil. *Lancet* 338(8760):167-169.

Betrán AP, Merialdi M, Lauer JA, Bing-Shun W, Thomas J, Van Look P, Wagner M (2007). Rates of Caesarean section: analysis of global, regional and national estimates. *Paediatr Perinat Epidemiol* 21(2): 98-113.

Blumenfeld YJ, El-Sayed YY, Lyell DJ, Nelson LM, and Butwick AJ (2015). Risk Factors for Prolonged Postpartum Length of Stay Following Cesarean Delivery. *Am J Perinatol* 32(9): 825–832.

Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J (2009). Bad bugs, no drugs: no ESKAPE! an update from the Infectious Diseases Society of America. *Clin Infect Dis* 48(1):1–12.

Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA (2013). Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health-Syst Pharm* 70(3):195-283.

Brink AJ, Messina AP, Feldman C, Richards GA, Becker PJ, Goff DA, Bauer KA, Nathwani D, van den Bergh D, on behalf of the Netcare Antimicrobial Stewardship Study Alliance (2016). Antimicrobial stewardship across 47 South African hospitals: An implementation study. *Lancet Infect Dis* 16(9):1017-1025.

Burke JP (2001). Maximizing Appropriate Antibiotic Prophylaxis for Surgical Patients: An Update from LDS Hospital, Salt Lake City. *Clin Infect Dis* 33(2):S78–83.

Calvert C, Ronsmans C (2013). HIV and the Risk of Direct Obstetric Complications: A Systematic Review and Meta-Analysis. *PLoS ONE* 8(10): e74848.

Campbell OMR, Calvert C, Testa A, Strehlow M, Benova L, Keyes E, Donnay F, Macleod D, Gabrysch S, Rong L, Ronsmans C, Sadruddin S, Koblinsky M, Bailey P (2016). The scale, scope, coverage, and capability of childbirth care. *Lancet* 388(10056):2193–2208.

Cecatti JG (2005). Antibiotic prophylaxis for Caesarean section: RHL commentary (last revised: 18 January 2005). *The WHO Reproductive Health Library*; Geneva: World Health Organization.

Centers for Disease Control and Prevention NNIS System (CDC) (2000). National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992–April 2000. *Am J Infect Control* 28(6):429–448.

Chaim W, Bashiri A, Bar-David J, Shoham-Vardi I, Mazor M (2000). Prevalence and clinical significance of postpartum endometritis and wound infection. *Infect Dis Obstet Gynecol* 8(2):77–82.

Costantine MM, Rahman M, Ghulmiyah L, Byers BD, Longo M, Wen T, Hankins GD, Saade GR (2008). Timing of perioperative antibiotics for cesarean delivery: a metaanalysis. *Am J Obstet Gynecol* 199(3):301.e1-6.

Council for Medical Schemes. Annual Report 2014/2015. Available at: [https://www.medicalschemes.com/files/Annual%20Reports/AR2014\\_2015.pdf](https://www.medicalschemes.com/files/Annual%20Reports/AR2014_2015.pdf). (Accessed on 25 October 2016).

Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM (2012). Race, ethnicity, and nativity differentials in pregnancy-related mortality in the United States: 1993–2006. *Obstet Gynecol* 120(2 Pt 1):261–268.

Cullinan K (2006). Health services in South Africa: A basic introduction. Health-e News Service. 2006. Available at <https://www.health-e.org.za>. (Accessed on 9 October 2016).

Dahlke JD, Mendez-Figueroa H, Rouse DJ, Berghella V, Baxter JK, Chauhan SP (2013). Evidence-based surgery for cesarean delivery: an updated systematic review. *Am J Obstet Gynecol* 209(4):294–306.

Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M (2013). Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 4:CD003543.

Day C and Gray A (2016). Health and related indicators. In Padarath A, King J, Mackie E, Casciola J (eds). *South African Health Review 2016*. Health Systems Trust: Durban, Available at: [http://www.hst.org.za/sites/default/files/Health\\_Indicators\\_0.pdf](http://www.hst.org.za/sites/default/files/Health_Indicators_0.pdf) (Accessed 19 September 2016).

Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM (2007). Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 44(2): 159-177.

Department of Health (2015). Guidelines for maternity care in South Africa, A manual for clinics, community health centres and district hospitals (draft). Department of Health: Pretoria.

Department of Health (2016). Guidelines for maternity care in South Africa, A manual for clinics, community health centres and district hospitals (Fourth Edition). Department of Health: Pretoria.

Dhar H, Al-Busaidi I, Rath B, Nimre EA, Sachdeva V, Hamdi I (2014). A Study of Post-Caesarean Section Wound Infections in a Regional Referral Hospital, Oman. *Sultan Qaboos University Med J* 14(2):e211-217

Diamond MP, Entman SS, Salyer SL, Vaughn WK, Boehm FH (1986). Increased risk of endometritis and wound infection after cesarean section in insulin-dependent diabetic women. *Am J Obstet Gynecol* 155(2):297–300.

Dlamini LD, Sekikubo M, Tumukunde J, Kojjo C, Ocen D, Wabule A and Kwizera A (2015). Antibiotic prophylaxis for Caesarean section at a Ugandan hospital: a randomised clinical trial evaluating the effect of administration time on the incidence of postoperative infections. *BMC Pregnancy Childbirth* 15:91

Domínguez I, Rosales R, Cabello A, Bavestrello L, Labarca J (2016). Evaluation of antimicrobial consumption in 15 Chilean hospitals: results of a collaborative work, 2013. *Rev Chilena Infectol* 33(3):307-312.

Duff P (1987). Prophylactic antibiotics for cesarean delivery: A simple cost-effective strategy for prevention of postoperative morbidity. *Am J Obstet Gynecol* 157(4):794-798.

Emmons SL, Krohn M, Jackson M, Eschenbach DA (1988). Development of wound infections among women undergoing cesarean section. *Obstet Gynecol* 72(4):559–564.

Enkin M, Enkin E, Chalmers I, Iemink E (1989). Prophylactic antibiotics in association with cesarean section. In Chalmers I, Enkin M, Keirse MJ (eds): *Effective Care in Pregnancy and Childbirth*. Oxford: University Press, pp 1246-1269.

European Centre for Disease Prevention and Control (ECDC) (2016). European Surveillance of Antimicrobial Consumption Network. Available at: <http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial-consumption/ESAC-Net/Pages/ESAC-Net.aspx>. (Accessed on 5 November 2016).

Faro S, Martens MG, Hammill HA, Riddle G, Tortolero G (1990). Antibiotic prophylaxis: Is there a difference? *Am J Obstet Gynecol* 162(4):900-909.

Farret TCF, Dalléb J, Monteiroc VDS, Riched CVW, Antonello VS (2015). Risk factors for surgical site infection following cesarean section in a Brazilian Women's Hospital: a case-control study. *Braz j infect dis* 19(2):113–117.

Faundes A, Cecatti JG (1991). Which policy for Caesarean section in Brazil? An analysis of trends and consequences. *Health Policy Plan* 8(1):33-42.

Ferrero S, Bentivoglio G (2003). Post-operative complications after Caesarean section in HIV-infected women. *Arch Gynecol Obstet* 268(4):268–273.

French R, Brocklehurst P (1998). The effect of pregnancy on survival in women infected with HIV a systematic review of the literature and meta-analysis. *Br J Obstet Gynaecol* 105(8): 827–835.

Galask RP (1987). Changing concepts in obstetric antibiotic prophylaxis. *Am J Obstet Gynecol* 157(2):491–497.

GBD 2015 SDG Collaborators (2016). Measuring the health-related Sustainable Development Goals in 188 countries: a baseline analysis from the Global Burden of Disease Study 2015. *Lancet* 388(10053):1813–1850.

GBD 2015 Maternal Mortality Collaborators (2016). Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 388(10053):1775–1812.

Gidiri MF, Ziruma A (2014). A randomized clinical trial evaluating prophylactic single-dose vs prolonged course of antibiotics for Caesarean section in a high HIV-prevalence setting. *J Obstet Gynaecol* 34(2):160-164.

Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J, Martone WJ (1996). Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership (consensus statement). *JAMA* 275(3):234–240.

Gonik B, McGregor J (1994). Comparison of Short Vs. Long Half-Life Single-Dose Prophylactic Antibiotics for Cesarean Section. *Infect Dis Obstet Gynecol* 2(3):120-125.

Goossens H, French M, van der Stichele R, Elseviers M (2005). Outpatient antibiotic use in Europe and association with resistance: across-national database study. *Lancet* 365(9459):579–587.

Gottlieb T, Nimmo GR (2011). Antibiotic resistance is an emerging threat to public health: an urgent call to action at the Antimicrobial Resistance Summit 2011. *Med J Aust* 194(6):281-283.

Gould D (2007). Caesarean section, surgical site infection and wound management. *Nurs Stand* 21(32):57–62.

Graham W, Hussein J (2003). Measuring and estimating maternal mortality in the era of HIV/AIDS. Workshop on HIV/AIDS and Adult mortality in developing countries. Available at: [http://www.un.org/esa/population/publications/adultmort/GRAHAM\\_Paper8.pdf](http://www.un.org/esa/population/publications/adultmort/GRAHAM_Paper8.pdf). Accessed on 24 October 2016.

Graham W, Woodd S, Byass P, Filippi V, Gon G, Virgo S, Chou D, Hounton S, Lozano R, Pattinson R, Singh S (2016). Diversity and divergence: the dynamic burden of poor maternal health. *Lancet* 388(10056):2164–2175.

Griggs D, Stafford-Smith M, Gaffney O, Rockström J, Ohman MC, Shyamsundar P, Steffen W, Glaser G, Kanie N, Noble I (2013). Policy: sustainable development goals for people and planet. *Nature* 495(7441):305–307.

Harrison D (2009). An overview of health and healthcare in South Africa 1994 – 2010: priorities, progress and prospects for new gains. Available at: <http://ftp.bhfglobal.com/files/bhf/overview1994-2010.pdf>. (Accessed on 09 October 2016).

Hedrick TL, Sawyer RG (2012). The end of postoperative antimicrobial prophylaxis? *Lancet Infect Dis* 12(5):357– 358.

Henderson E, Love EJ (1995). Incidence of hospital-acquired infections associated with Caesarean section. *J Hosp Infect* 29(4):245–55.

Hepler CD, Strand LM (1990). Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm* 47(3):533-543.

Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, Guerin PJ, Piddock LJ (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 387(10014):176–187.

Hopkins L, Smaill F (2000). Antibiotic prophylaxis regimens and drugs for cesarean section. *Cochrane Database Syst Rev* 2:CD001136.

Jobson M (2015). Structure of the health system in South Africa. Khulumani Support Group. Available at: <http://www.khulumani.net/>. (Accessed on 7 October 2016).

Johannsson B, Beekmann SE, Srinivasan A, Hersh AL, Laxminarayan R, Polgreen PM (2011). Improving antimicrobial stewardship: the evolution of programmatic strategies and barriers. *Infect Control Hosp Epidemiol* 32(4):367–374.

Kaimal AJ, Zlatnik MG, Cheng YW, Thiet MP, Connatty E, Creedy P, Caughey AB (2008). Effect of change in policy regarding the timing of prophylactic antibiotics on the rate of post Caesarean delivery surgical-site infections. *Am J Obstet Gynecol* 199(3):310.e1–5.

Kalogeropoulos A (2014). Understanding Retrospective vs. Prospective Study designs. Emory clinical cardiovascular research institute. Emory University. Available at: <http://medicine.emory.edu/documents/research/kalogeropoulos-study-design-talk.pdf>. Accessed on 8 October 2016.

Keski-Nisula L, Kirkinen P, Katila ML, Ollikainen M, Suonio S, Saarikoski S (1997). Amniotic fluid U. urealyticum colonization: significance for maternal peripartal infections at term. *Am J Perinatol* 14(3):151–156.

Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ (1999). The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infect Control Hosp Epidemiol* 20(11):725–730.

Koblinsky M, Moyer CA, Calvert C, Campbell J, Campbell O, Feigl AB, Graham WJ, Hatt L, Hodgins S, Matthews Z, McDougall L, Moran AC, Nandakumar AK, Langer A (2016). Quality maternity care for every woman, everywhere: a call to action. *Lancet* 388(10057): 2307–2320.

Kuklina EV, Meikle SF, Jamieson DJ, Whiteman MK, Barfield WD, Hillis SD, Posner SF (2009). Severe obstetric morbidity in the United States: 1998–2005. *Obstet Gynecol* 113(2 Pt 1):293–299.

Lamont R, Sobel J, Kusanovic J, Vaisbuch E, Mazaki-Tovi S, Kim S, Uldbjerg N, Romero R (2011). Current debate on the use of antibiotic prophylaxis for Caesarean section. *Obstet Gynecol* 118(2):193–201.

Lanbeck P, Ragnarson TG, Resman F (2016). A cost analysis of introducing an infectious disease specialist- guided antimicrobial stewardship in an area with relatively low prevalence of antimicrobial resistance. *BMC Health Serv Res* 16:311.

Lautenbach E, Weiner MG, Nachamkin I, Bilker WB, Sheridan A, Fishman NO (2006). Imipenem resistance among *Pseudomonas aeruginosa* isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. *Infect Control Hosp Epidemiol* 27(9):893–900.

Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O (2013). Antibiotic resistance-the need for global solutions. *Lancet Infect Dis* 13(12):1057–1098.

Ledger WJ (1986). *Infection in the Female*. Philadelphia: Lea & Febiger, pp 113-120.

Liu R, Lin L, Wang D (2016). Antimicrobial prophylaxis in Caesarean section delivery. *Exp Ther Med* 12(2): 961-964.

Livermore D, Hope R, Reynolds R, Blackburn R, Johnson A, Woodford N (2013). Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream *Enterobacteriaceae* from the UK: links to prescribing change? *J Antimicrob Chemother* 68(11):2667–2674.



Lyimo FM, Massinde AN, Kidenya BR, Konje E, Mshana SE (2013). Single dose of gentamicin in combination with metronidazole versus multiple doses for prevention of post-Caesarean infection at Bugando Medical Centre in Mwanza, Tanzania: a randomized, equivalence, controlled trial. *BMC Pregnancy Childbirth* 13:123.

MacDougall C, Polk RE (2005). Antimicrobial stewardship programs in healthcare systems. *Clin Microbiol Rev* 18(4):638–656.

Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR (1999). Guideline for prevention of surgical site infection. Hospital infection controlpractices advisory committee. *Infect Control Hosp Epidemiol* 20(4):250–278.

Martens MG, Kolrud BL, Faro S, Maccato M, Hammill H (1995). Development of wound infection or separation after cesarean delivery. Prospective evaluation of 2,431 cases. *J Reprod Med* 40(3):171–175.

Matuschka PR, Cheadle WG, Burke JD, Garrison RN (1997). A new standard of care: administration of preoperative antibiotics in the operating room. *Am Surg* 63(6):500–503.

Minister of Health (2015). White Paper on National Health Insurance. Government Notice No. 1230, Government Gazette No. 39506, 11 December 2015. Available at [http://www.gov.za/sites/www.gov.za/files/39506\\_gon1230.pdf](http://www.gov.za/sites/www.gov.za/files/39506_gon1230.pdf). (Accessed on 3 November 2016).

Mitt P, Lang K, Peri A, Maimets M (2005). Surgical-site infections following cesarean section in an Estonian university hospital:postdischarge surveillance and analysis of risk factors. *Infect Control Hosp Epidemiol* 26(5):449–454.

Moodliar S, Moodley J, Esterhuizen TM (2007). Complications associated with Caesarean delivery in a setting with high HIV prevalence rates. *Eur J Obstet Gynecol Reprod Biol* 131(2):138–145.

Morisaki N, Ganchimeg T, Ota E, Vogel JP, Souza JP, Mori R, Gülmezoglu AM, on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network (2014). Maternal and institutional characteristics associated with the administration of prophylactic

antibiotics for Caesarean section: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG* 121(1): 66–75.

Mugford M, Kingston J, Chalmers I (1989). Reducing the incidence of infection after Caesarean section: implications of prophylaxis with antibiotics for hospital resources. *BMJ* 299(6706):1003-1006.

Naidoo RP, Moodley J (2009). Rising rates of Caesarean sections: an audit of Caesarean sections in a specialist private practice. *SA Fam Pract* 51(3):254-258.

National Department of Health (NDOH) (2012). Standard Treatment Guidelines (STGs) and Essential Medicines List: A Hospital Level. National Department of Health: Pretoria, 11.1-11.2.

National Department of Health (NDOH) (2015). The 2013 National Antenatal Sentinel HIV Prevalence Survey South Africa. National Department of Health: Pretoria.

Navarro R, (2009). Chapter 8: Drug Utilization Review Strategies. In *Managed Care Pharmacy Practice*, Jones & Bartlett Publishers, Massachusetts, pp. 215 – 229.

NCCEMD (2016). Saving Mothers 2011-2013: Sixth report on the Confidential Enquiries into Maternal Deaths in South Africa. Available at <https://www.health-e.org.za/2016/05/06/report-saving-mothers-2011-2013/>. (Accessed on 12 October 2016).

Newton ER, Wallace PA (1998). Effects of prophylactic antibiotics on endometrial flora in women with post cesarean endometritis. *Obstet Gynecol* 92(2):262–268.

Nwankwo EO, Ibeh I, Enabulele OI (2012). Incidence and risk factors of surgical site infection in a tertiary health institution in Kano, north-western Nigeria. *Int J Infect Control* 8(4):1–6.

Oliveira CO, Ciosak SI (2004). Infection of surgical site in the following postdischarge: impact in the incidence and evaluation of the used methods. *Rev Esc Enferm USP* 38(4):379–385.

Olsen MA, Butler AM, Willers DM, Devkota P, Gross GA, Fraser VJ (2008). Risk factors for surgical site infection after low transverse cesarean section. *Infect Control Hosp Epidemiol* 29(6):477–884.

Owens R Jr (2008). Antimicrobial stewardship: concepts and strategies in the 21st century. *Diagn. Microbiol Infect Dis* 61(1):110–128.

Public Health Agency of Sweden (2014). Swedish work on containment of antibiotic resistance. Available at: <https://www.folkhalsomyndigheten.se/pagefiles/17351/Swedish-work-on-containment-of-antibiotic-resistance.pdf>. (Accessed on: 05 November 2016).

Raleigh VS, Cooper J, Bremner SA, Scobie S (2008). Patient safety indicators for England from hospital administrative data: case-control analysis and comparison with US data. *BMJ* 337:a1702.

Robinson G, Wilson SE, Williams RA (1987). Surgery in patients with acquired immunodeficiency syndrome. *Arch Surg* 122(2):170–175.

Rodriguez EJ, Spann C, Jamieson D, Lindsay M (2001). Post operative morbidity associated with Caesarean delivery among human immunodeficiency virus-seropositive women. *Am J Obstet Gynecol* 184(6):1108-1111.

Ronsmans C, Holtz S, Stanton C (2006). Socioeconomic differentials in Caesarean rates in developing countries: a retrospective analysis. *Lancet* 368(9546): 1516–1523.

Salim R, Braverman M, Berkovic I, Suliman A, Teitler N, Shalev E (2011). Effect of interventions in reducing the rate of infection after cesarean delivery. *Am J Infect Control* 39(10):e73–78.

Schellack N, Pretorius R, Messina AP (2016). ‘*Esprit de corps*’: Towards collaborative integration of pharmacists and nurses into antimicrobial stewardship programmes in South Africa. *S Afr Med J* 106(10):973-974.

Semprini AE, Castagna C, Ravizza M, Fiore S, Savasi V, Muggiasca ML, Grossi E, Guerra B, Tibaldi C, Scaravelli G, Prati E, Pardi G (1995). The incidence of complications after Caesarean section in 156 HIV-positive women. *AIDS* 9(8):913–917.

Shakya A, Sharma J (2010). Comparison of single versus multiple doses of antibiotic prophylaxis in reducing post-elective Caesarean section infectious morbidity. *Kathmandu Univ Med J* 8(30):179–184.

Shaw D, Guise J, Shah N, Gemzell-Danielsson K, Joseph KS, Levy B, Wong F, Woodd S, Main EK (2016). Drivers of maternity care in high-income countries: can health systems support woman-centred care? *Lancet* 388(10057): 2282–2295.

Shlaes DM, Gerding DN, John JF Jr, Craig WA, Bornstein DL, Duncan RA, Eckman MR, Farrer WE, Greene WH, Lorian V, Levy S, McGowan JE Jr, Paul SM, Ruskin J, Tenover FC, Watanakunakorn C (1997). Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. *Infect Control Hosp Epidemiol* 18(4): 275-291.

Silver A, Eichorn A, Kral J, Pickett G, Barie P, Pryor V, Dearie MB (1996). Timeliness and use of antibiotic prophylaxis in selected inpatient surgical procedures: The antibiotic prophylaxis study group. *Am J Surg* 171(6):548–552.

Slobogean GP, O'Brien PJ, Brauer CA (2010). Single-dose versus multiple-dose antibiotic prophylaxis for the surgical treatment of closed fractures. *Acta Orthop* 81(2):256–262.

Smaill FM, Grivell RM (2014). Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. *Cochrane Database Syst Rev* 10:CD007482.

Smaill FM, Gyte GM (2010). Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. *Cochrane Database Syst Rev* 1:CD007482.

Smaill F, Hofmeyr GJ (2002). Antibiotic prophylaxis for Caesarean section. *Cochrane Database Syst Rev* 3: CD000933.

Smyth ET, Emmerson AM (2000). Surgical site infection surveillance. *J Hosp Infect* 45(3):173–184.

Snyman L (2002). Is the high Caesarean section rate a cause for concern? *Obstet Gynaecol Forum* 12(2):8–13.

Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS) (2012). Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infect Control Hosp Epidemiol* 33(4):322–327.

Statistics South Africa (2015). Mid-year population estimates 2015. Statistical release P0302. Statistics SA: Pretoria.

Tshibangu KC, De Jongh MA, De Villiers DJ, Du Toit JJ, Shah SMH (2002). Incidence and outcome of Caesarean section in the private sector – 3 year experience at Pretoria Gynaecological Hospital. *S Afr Med J* 92(12):956–959.

UNICEF (2008). Basic Indicators 2008. Available at: [http://www.unicef.org/spanish/rightsite/sowc/pdfs/statistics/SOWC\\_Spec\\_Ed\\_CRC\\_TABLE%201.%20BASIC%20INDICATORS\\_EN\\_111309.pdf](http://www.unicef.org/spanish/rightsite/sowc/pdfs/statistics/SOWC_Spec_Ed_CRC_TABLE%201.%20BASIC%20INDICATORS_EN_111309.pdf). (Accessed on 15 September 2016).

United Nations (2015a). Transforming our world: the 2030 Agenda for Sustainable Development. New York: United Nations, 2015. Available at: <https://sustainabledevelopment.un.org/post2015/transformingourworld>. (Accessed on 9 October 2016).

United Nations (2015b). Millennium Development Goals and Beyond. Available at: [www.un.org/millenniumgoals/](http://www.un.org/millenniumgoals/). (Accessed on 11 October 2016).

Van Dillen J, Zwart J, Schutte J, van Roosmalen J (2010). Maternal sepsis: epidemiology, etiology and outcome. *Curr Opin Infect Dis* 23(3):249–254.

Verkuyt DAA (1995). Practising obstetrics and gynaecology in areas with a high prevalence of HIV infection. *Lancet* 346(8970):293–296.

Vuolo JC (2006). Assessment and management of surgical wounds in clinical practice. *Nurs Stand* 20(52):46–58.

Warnecke HH, Graeff H, Selbmann HK, Preac-Mursic V, Adam D, Gloning KP, Jänicke F, Zander J (1982). Perioperative short-term prophylaxis with antibiotics in Caesarean section. *Geburtshilfe Frauenheilkd* 42(9):654–661. (In German).

Watts DH, Krohn MA, Hillier SL, Eschenbach DA (1990). Bacterial vaginosis as a risk factor for post-cesarean endometritis. *Obstet Gynecol* 75(1):52–58.

Wloch C, Wilson J, Lamagni T, Harrington P, Charlett A, Sheridan E (2012). Risk factors for surgical site infection following Caesarean section in England: Results from a multicentre cohort study. *BJOG* 119(11):1324–1333.

World Health Organization (1985). Appropriate technology for birth. *Lancet* 2(8452): 436–437.

World Health Organization (2001). WHO global strategy for containment of antimicrobial resistance. World Health Organization, Geneva. Available at [http://www.who.int/csr/resources/publications/drugresist/WHO\\_CDS\\_CSR\\_DRS\\_2001\\_2\\_EN/en/](http://www.who.int/csr/resources/publications/drugresist/WHO_CDS_CSR_DRS_2001_2_EN/en/). (Accessed 10 October 2016).

World Health Organization (2003). Introduction to Drug Utilization Research. World Health Organization: Geneva. Available at <http://apps.who.int/medicinedocs/en/d/Js4876e/>. (Accessed 14 July 2015).

World Health Organization (2010). The global numbers and costs of additionally needed and unnecessary Caesarean sections performed per year: overuse as a barrier to universal coverage. World Health Report 2010. World Health Organization: Geneva. Available at: <http://www.who.int/healthsystems/topics/financing/healthreport/30C-sectioncosts.pdf>. (Accessed on 1 September 2016).

World Health Organization (2014). Antimicrobial Resistance: Global Report on Surveillance. World Health Organization: Geneva. Available at: <http://www.who.int/drugresistance/documents/surveillancereport/en/>. (Accessed on 25 September 2016).

World Health Organization (2015). Antimicrobial resistance Fact sheet No. 194. World Health Organization: Geneva. Available at: <http://www.who.int/mediacentre/factsheets/fs194/en/>. (Accessed on 23 September 2016).

World Health Organization (2016a). Global Strategy for Women's, Children's and Adolescents' Health, 2016–2030. World Health Organization: Geneva. Available at <http://www.who.int/life-course/partners/global-strategy/global-strategy-2016-2030/en/>. (Accessed on 10 October 2016).

World Health Organization (2016b). Global guidelines for the prevention of surgical site infection. Available at: <http://www.who.int/gpsc/ssi-prevention-guidelines/en/>. (Accessed on 4 November 2016).

## **APPENDICES**



## **APPENDIX 1: INTERVIEW SCHEDULE**

1. What has been your experience regarding post-Caesarean section infections in women delivered in the Heidelberg Hospital maternity ward?  

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2. Have any of your experiences affected your prescribing practices in relation to antibiotic prophylaxis in Caesarean sections?  

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3. Is there a protocol in place for the administration of antibiotic prophylaxis in patients undergoing CS at Heidelberg Hospital?  

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4. Are you familiar with the antibiotic prophylaxis recommendations included in the National Department of Health Standard Treatment Guidelines (Adult Hospital edition 2012)?  

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5. What antibiotic prophylaxis regimen do you use in CS?  

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6. What doses are prescribed and for what duration?  

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7. Are there specific reasons why you chose this regimen and this duration?  

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8. What doses are used for HIV-positive patients and why?  

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9. How would you feel about having to follow a different prophylactic regimen from that stated in the NDOH STGs?  

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10. What changes or recommendations would you suggest for consideration in the Standard Treatment Guidelines regarding antibiotic prophylaxis in CS?  

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## APPENDIX 2: INFORMATION SHEET AND CONSENT TO PARTICIPATE

Date:

Good day participant

My name is Seshnee Govender and I am a Pharmacist currently working at Heidelberg Hospital.

You are being invited to consider participating in a study that involves obtaining information about the use of antibiotic prophylaxis in patients undergoing Caesarean section.

This form details the purpose of this study, a description of the involvement required and your rights as a participant.

The study is expected to enrol all medical practitioners involved in the management of these patients in the maternity ward at Heidelberg Hospital.

### **The purpose of this study:**

The purpose of this study is to contribute to the rational and responsible use of medicines, in particular antibiotics, through the application of medicines use evaluation. The overall aim is to help health care facilities to understand, interpret and improve the prescribing, administration and use of medications, in a primary level hospital setting.

### **The methods that will be used to meet this purpose include:**

Individual interviews with an estimated length of half an hour will be used. The interview will be tape recorded, if you give permission. You will be asked a series of questions regarding your experiences and the use of antibiotic prophylaxis in patients undergoing Caesarean sections. You are not obligated to answer the questions should be feel at all uncomfortable. You will also be free to withdraw your consent to participate at any time.

### **The benefits and risks of the research will be:**

The benefit of your participation is that you will contribute information on the antibiotic prophylaxis regimen used. This will help in improving the prescribing and administration of antibiotics. There are no patient risks associated with this study as it does not affect patient care. Your confidentiality will be protected at all times and your name will not be linked with the data or reported in any way.

## APPENDIX 2: CONTINUED...

This study has been reviewed and approved by the UKZN Biomedical Research Ethics Committee (approval number\_\_\_\_\_).

A summary of the results will be available to participants upon request. Please contact interviewer, Seshnee, with any questions or concerns on (016) 3411100 or 0790860268 alternatively email on [sesh.govender101@gmail.com](mailto:sesh.govender101@gmail.com)

Or contact the UKZN Biomedical Research Ethics Committee on:

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Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: [BREC@ukzn.ac.za](mailto:BREC@ukzn.ac.za)

### **Subject's Understanding**

- Participation is voluntary and you have the right to withdraw at any point in time with no adverse repercussions
- There will be no potential consequences should the participant decide to withdraw and all information provided will be destroyed and omitted from the final report
- There will be no costs incurred as a result of participating in this study
- All data collected will be limited to this use or other research-related usage as authorized by the University of KwaZulu-Natal.

Participants will not be identified by name or any identifying information in the final written report. All records will be kept confidential in the secure possession of the researcher. Individual responses will not be disclosed to anyone other than the research supervisor.

## **APPENDIX 2: CONTINUED...**

### **CONSENT**

I \_\_\_\_\_ have been informed about the study entitled "Antibiotic prophylaxis in a primary level hospital: A medicines use evaluation to assess compliance in caesarean sections" by Seshnee Govender.

I understand the purpose and procedures of the study.

I have been given an opportunity to answer questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher on the contact details provided above.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

### **BIOMEDICAL RESEARCH ETHICS ADMINISTRATION**

Research Office, Westville Campus  
Govan Mbeki Building  
Private Bag X 54001  
Durban  
4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: [BRECE@ukzn.ac.za](mailto:BRECE@ukzn.ac.za)

## APPENDIX 2: CONTINUED...

By signing below you agree that you have read and understood the above information, consent to participating in this study, and to the recording of the interview.

_____	_____
Signature of Participant	Date

_____	_____
Signature of Witness	Date
(Where applicable)	

_____	_____
Signature of Translator	Date
(Where applicable)	

### APPENDIX 3: MEDICINE USE EVALUATION DATA CAPTURE SHEET

[illegible]

#### APPENDIX 4: INTERVIEW SCHEDULE (CLOSED-ENDED)

1. What has been your experience regarding post-Caesarean section infections in women delivered in the Heidelberg Hospital maternity ward?

*Common* ☐ *Rare* ☐

2. Have any of your experiences affected your prescribing practices in relation to antibiotic prophylaxis in Caesarean sections?

*Yes* ☐ *No* ☐

3. Is there a protocol in place for the administration of antibiotic prophylaxis in patients undergoing CS at Heidelberg Hospital?

*Yes* ☐ *No* ☐ *Not Sure* ☐

4. Are you familiar with the antibiotic prophylaxis recommendations included in the National Department of Health Standard Treatment Guidelines (Adult Hospital edition 2012)?

*Yes* ☐ *No* ☐

5. What pre and post antibiotic prophylaxis regimen do you use in CS?

*Pre-op:* *Cefazolin 1g IVI*

*Post-op:* *Cefazolin*

*Post-discharge: Amoxicillin & Metronidazole*

6. What doses are prescribed and for what duration?

***Pre-op:*** *1g* *< 60 minutes before the first incision*

***Post-op:*** *1g* *8 hourly IVI* *over 24 hour period (3 Doses)*

***Post-discharge:***

*Amoxicillin* *500mg 8hourly P.O over a 5 day period*

*Metronidazole* *400mg 8hourly P.O over a 5 day period*

7. Are there specific reasons why you chose this regimen and this duration?

Yes ☐ please specify: \_\_\_\_\_ No ☐

8. What doses are used for HIV-positive patients and why?

*Pre-op: Cefazolin 1g IVI < 60 minutes before the first incision*

*Post-op: Cefazolin 1g every 8 hours IVI for 3 days (9 doses)*

*Metronidazole 500mg every 8 hours IVI for 3 days (9 doses)*

*Post-discharge: Amoxicillin 500mg every 8 hours P.O for 5 days*

*Metronidazole 400mg every 8 hours P.O for 5 days*

*The CD4 count is not always available and patients are immunocompromised.*

9. How would you feel about having to follow a different prophylactic regimen from that stated in the NDOH STGs?

*Willing to follow new recommendation provided there is evidence based research* ☐

*Not willing since there is no problems with the current regimen* ☐

10. Would you suggest any changes or recommendations for consideration in the Standard Treatment Guidelines regarding antibiotic prophylaxis in CS?

Yes ☐ please specify: \_\_\_\_\_ No ☐



## APPENDIX 5: CONDITIONAL APPROVAL LETTER FROM HEIDELBERG HOSPITAL



### HEIDELBERG HOSPITAL

Enquiries: L.F. van der Ende  
Telephone number: (016) 341-1286  
Fax/Email: 0852708744  
Email: [Louise.vanderende@gauteng.gov.za](mailto:Louise.vanderende@gauteng.gov.za)

The Biomedical Research Ethics committee  
University of KZN  
WESTVILLE

REQUEST TO EMBARK ON POST GRADUATE RESEARCH:  
S. GOVENDER  
STUDENT NO: 209505712

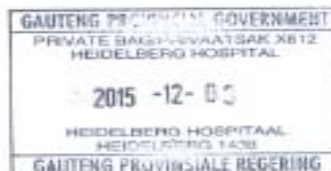
This is to confirm that Ms. S. Govender: Persal no. 64714012 has requested permission from Heidelberg hospital to embark on performing her Master's Degree at the University of KZN.

Heidelberg hospital is aware of the above request and awaits approval from UKZN after which the Gauteng Department of Health: Research department will approve her request to use data from Heidelberg hospital.

Regards

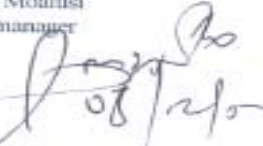
Recommended by:

  
Mr. B. Mierwa  
Pharmacy manager  
Date: 03/12/2015



Supported by:

Dr. M.B. Moalusi  
Clinical manager  
Date:



Heidelberg Hospital  
Hospital street  
HEIDELBERG  
1441

Private Bag 612  
HEIDELBERG  
1441

**APPENDIX 6: CONDITIONAL APPROVAL LETTER FROM THE GAUTENG  
DEPARTMENT OF HEALTH**



**GAUTENG PROVINCE**  
HEALTH  
REPUBLIC OF SOUTH AFRICA

The Biomedical Research Ethics Committee

University of KZN

Westville

Re: Conditional approval for research pending ethics approval

This serves to notify you that that the Department of Health has reviewed the research of Ms Seshnee Govender on "Antibiotic prophylaxis in a primary level hospital: a medicines use evaluation to assess compliance in caesarean sections" and agrees that the study be conducted at Heidelberg hospital in Gauteng province.

The research question of "In women undergoing caesarean sections at Heidelberg Hospital, is the correct choice of antibiotic and duration of antibiotic prophylaxis being administered, according to the South African National Standard Treatment Guidelines, and if not, what are the reasons for this noncompliance" is relevant falls within the research priorities of the Gauteng Department of Health.

The findings will strengthen the knowledge of health care facilities to understand, interpret and improve the prescribing, administration and use of medications, in a primary level hospital setting.

The Department therefore grants provisional approval for this study pending ethics approval.

Kind Regards

Dr Bridget Ikalafeng

Research and Epidemiology Manager

Date: 30/06/2016

## APPENDIX 7: ETHICAL APPROVAL FROM THE BIOMEDICAL RESEARCH ETHICS COMMITTEE OF THE FACULTY OF HEALTH SCIENCES, UNIVERSITY OF KWAZULU-NATAL



06 July 2016

Ms S Govender (209505712)  
School of Pharmacy  
College of Health Sciences  
[Sashit.govender101@gmail.com](mailto:Sashit.govender101@gmail.com)

Protocol: Antibiotic prophylaxis in a primary level hospital: A medicines use evaluation to assess compliance in caesarean sections.  
Degree: MSc (Pharm)  
BREC reference number: BE508/15

### EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 09 December 2015.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 01 July 2016 to queries raised on 25 February 2016 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from 06 July 2016. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be RATIFIED by a full Committee at its meeting taking place on 16 August 2016.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

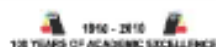
Yours sincerely

  
Professor J Tsoka-Gwegweni  
Chair: Biomedical Research Ethics Committee

cc: supervisor: [stony18@ukzn.ac.za](mailto:stony18@ukzn.ac.za)  
cc: postgrad: [stony18@ukzn.ac.za](mailto:stony18@ukzn.ac.za)

Biomedical Research Ethics Committee  
Professor J Tsoka-Gwegweni (Chair)  
Westville Campus, Govan Mbeki Building  
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Telephone: +27 (0) 31 260 2486 Facsimile: +27 (0) 31 260 4909 Email: [brec@ukzn.ac.za](mailto:brec@ukzn.ac.za)  
Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>



Founding Communities:  Edendale  Howard College  Medical School  Pietermaritzburg  Westville